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SEPTEMBER 1954
VOLUME 72 NUMBER 3

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 7, 1919, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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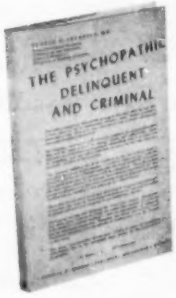

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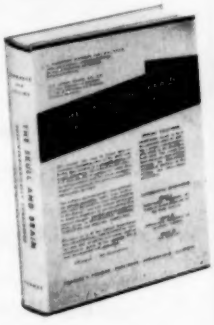

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EXPERIMENTAL OBSERVATIONS ON "PSYCHOSOMATIC" MECHANISMS

I. Gastrointestinal Disturbances

J. D. FRENCH, M.D.
R. W. PORTER, M.D., Ph.D.
E. B. CAVANAUGH, A.B.
AND
R. L. LONGMIRE, A.B.
LONG BEACH, CALIF.

VISCERAL and somatic abnormalities suspected of resulting from disordered function of the normal brain have long been known as "psychosomatic" diseases or, perhaps, diseases of "stress." Opinion exists, indeed, that a great many diseases result from, or are strongly influenced by, psychological reactions unsuitable to normal existence. Even expressions of a more conservative attitude concede, with some consistency, a connection between cerebral function and certain visceral ailments, prominent among which are peptic ulcer, hypertension, and ulcerative colitis. Speculation concerning possible relationship between cause and effect in such instances has resulted principally from clinical analysis of these disorders, particularly from the results of therapeutic attack on the autonomic nervous system in patients suffering from them.

For obvious reasons, examination of "psychosomatic" disorders in experimental animals is extremely difficult. Intercommunication between examiner and subject is impossible and extrapolation of observation to man hazardous. Moreover, disorders of the nature of those used as examples do not exist natively in animals, and attempts to produce them are unsuccessful in the main, short of introducing such alteration in physiological function as to make interpretation questionable.

It is clearly evident experimentally that the central nervous system is capable of exerting both normal and deleterious influences on visceral structures. In this regard, it is possible to excite the stomach to secrete hydrochloric acid by stimulation in either the anterior or the posterior hypothalamus.* Moreover, acute hemorrhagic or ulcerative lesions can be produced in the gastrointestinal tract of monkeys and cats by electrolytic lesions appropriately placed in the same regions. As the hypothalamus is known, therefore, not only to be involved intimately with visceral functions but also to have rich connections with the rest of the brain, it can be reasoned

From the Veterans Administration Hospital, Long Beach, and the Departments of Surgery and Anatomy, University of California School of Medicine at Los Angeles.

Mary Wiley and Robert Rogers performed the experiments and Mary Brown made the histological preparations.

Aided by grants from the Commonwealth Fund; Smith, Kline & French Laboratories, and the National Institute of Neurological Diseases and Blindness, United States Public Health Service.

* References 1 and 2.

a priori that investigations of this region regarding neurogenic influences in association with visceral disease might be singularly fruitful.

If, as seems likely, the brain can exert unusual stress upon the hypothalamus, and through deleterious influences thereby excited in it induce visceral disease, chronic experimental stimulation of this hypothalamic region should result in comparable changes. Moreover, perhaps such chronic excitation would be expected to simulate abnormal processes naturally resulting in these disorders far more significantly than have other experimental measures which induce profoundly altered physiological states and improbable etiological conditions in the animals.

For these reasons long-term observations were made on monkeys in which the hypothalamic part of the brain was stimulated daily through chronically implanted electrodes. The changes induced in the stomach of these animals form the subject matter for this report.

METHODS

Experiments were performed on 17 healthy monkeys (Macacus mulattus), of which 7 were female. With the animal under pentobarbital (Nembutal) anesthesia, a single bipolar electrode was oriented stereotaxically in the hypothalamus or, for control, in another area of the cephalic brain stem. The electrodes consisted of a pair of 0.005 in. stainless steel wires (gold-plated), insulated except for 1 mm. at the tip and attached by enamel for 1 cm. to the end of a rigid nichrome wire strut. The strut wire was passed through a drill hole in the calvaria to the appropriate setting by means of the Horsley-Clarke apparatus, and the pliable electrodes, freely mobile outside the head, were soldered to insulated lead cables 0.5 to 1 cm. from the point of exit. These cables were delivered through the skin through a stab wound in the suboccipital region and tensed so that lead wire and cables lay snugly along the external surface of the calvaria. Liquid Kadon was then poured into the drill hole around the strut, so that when it hardened the strut carrying the electrodes was held securely in place and could be cut off. The curvilinear scalp incision was then closed in layers. The lead-off wires were threaded through the links of a pet leash and attached to a simple harness on the animal and, distally, to the cage, from which point of exit they were conducted to the stimulator located in an adjoining room. After the operation the resistance of the conducting system was tested with an ohmmeter, and a short strip of EEG tracing was made from the lead wires to verify a good hypothalamic contact of the electrodes.

Upon recovery from the operation the animals were placed together in a block of individual cages so that their external environment would be essentially identical. All were fed a normal diet and were subjected to the same observations, handling, and test conditions.

During the experiment stimuli (4 volts, 20 cps, 1 σ) were delivered to the test animals from a Grass square-wave stimulator two to four times a day, depending upon freedom from mechanical difficulties of individual lead connections. The response of each animal to stimulation and the state of his general physical fitness were noted daily. Each was weighed and had a stool examination for occult blood once weekly. Before stimulation was commenced and three to five weeks later, each animal had a gastric analysis under chloralosane anesthesia, at which time stomach contents aspirated through a Levin tube were tested for hydrochloric acid before and for four hours after excitation of the hypothalamus.

The conditions of the experiment were such that, for analysis, the animals were assigned to three groups; all groups, however, received identical treatment except as described here. One group, of 10 animals, received adequate daily stimulation for 30 to 74 days; another group, of 3, which had poor stimulation records (generally less than one a day) but which survived 25 to 77 days, were continued to control the effect of the indwelling electrode alone; a third group, of 4, survived only 6 to 14 days, usually with poor stimulation records, and served to control early effects of the operation and initial, rather vigorous manipulation.

All animals were killed because of irreparably broken electrode leads, because of illness thought to be significant to the experiment, or for examination after prolonged stimulation. Complete autopsies were made, appropriate tissues being preserved for photography and for microscopic examination. This report will concern itself primarily with changes noted in the

upper gastrointestinal tract; other observations are awaiting later description. In each instance the brain was carefully examined and the electrode placement was verified anatomically.

RESULTS

Gastrointestinal Lesions.—Six of the 10 test animals and none of the 7 controls developed significant gross lesions in the upper gastrointestinal tract (Table 1). Of the lesions which developed, four were sharply localized in the prepyloric and postpyloric region (Figs. 1 and 2), and two were generalized throughout the stomach (Fig. 3; Monkeys 44 and 33). One of the localized lesions was a lytic perforation of the duodenum (Fig. 3; Monkey 30). Two, essentially identical with each other in appearance, exhibited sharply demarcated margins from an otherwise normal stomach, both being located in the gastric antrum (Fig. 1). They existed as large (3 cm.) raised, edematous lesions, with deep purple coloration and a gray, necrotic

TABLE 1.—*Summary of Data on All Adequately Stimulated Animals**

CHRONIC STIMULATION BRAIN STEM OF MONKEYS

	ANIMAL	PLACEMENT	SURVIVAL DAYS	AV. STIM. PER DAY	WT. LOSS OR GAIN LBS.	G.I. LESION
	30	P	30	2.9	0	PERFORATED DUODENUM
LOCAL LESION	35	P	55	1.3	− .25	ANTRUM
	36	A	70	2.4	+ .75	ANTRUM
	40	A	69	2.4	0	ANTRUM
DIFFUSE LESION	33	P	71	2.2	+ .25	STOMACH
	44	A	56	2.4	+ 1.25	STOMACH
	28	P	74	2.2	− 1.25	0
NO LESION	29	A	65	2.3	+ .75	0
	43	P	55	2.8	− .75	0
	45	P	54	3.1	− .75	0

* Gross designation of stimulation sites are indicated in column marked "Placement," *P* referring to posterior hypothalamus and *A* to anterior hypothalamus.

center. The abnormality in the fourth animal was similar in location, color, and appearance to those just described, except that it was much smaller and less well developed (Fig. 2). The stomachs of two animals (Monkeys 33 and 44) displayed diffuse abnormality rather than local change. They were dilated and thin-walled and exhibited poor tone. The mucosae appeared to be both atrophic and edematous, presenting a mottled purple-gray appearance that was distinctly different from the normal. The upper gastrointestinal tracts of the remaining four test animals and of the seven controls were quite normal in appearance.

Electrode Placements.—The sites of electrode placements in the brains of all animals are summarized in Figure 4. Characteristic of placements in animals which developed focal abnormalities in the stomach was their tendency toward low midline grouping in the ventral diencephalon (Fig. 5). The monkey which developed a

perforation of the duodenum (Monkey 30) was stimulated in the intermammillary region. In two other animals the electrode was located in the preoptic area, while in the fourth (Monkey 35) it was situated low in the reticular formation just posterior to the mammillary bodies. In one animal, with diffuse change in the stomach (Monkey 33), the stimulus had been applied to a region near, but dorsal to, this latter area, while in the other (Monkey 44) the electrode was lodged in the dorsal periventricular region, just behind the anterior commissure.

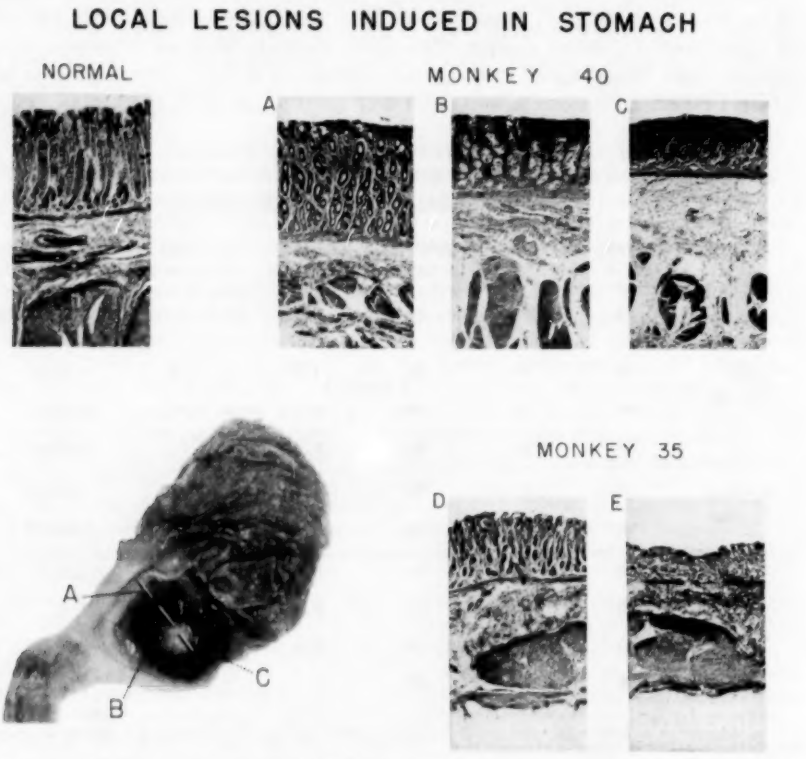

Fig. 1.—Photograph of the stomach of Monkey 40 (lower left) shows a lesion in the pyloric antrum. Photomicrographs *A*, *B*, and *C* were made from regions similarly designated in the photograph. The gross lesion in Monkey 35 was identical with that shown here, and photomicrographs *D* and *E* correspond to *A* and *C* in Monkey 40.

Locations of the electrodes in the four animals which received comparable stimulus but did not develop pathological changes in the upper gastrointestinal tract were, in general, dorsolateral or ventroposterior to this median axis. The electrodes were situated at random throughout the general area described in the remaining seven animals which received inadequate stimulation (Fig. 4), but in none of these did abnormality of the stomach or duodenum develop.

Residence of the electrode within the brain, per se, induced no reactive change which was visible grossly, and microscopic alteration was minimal (Fig. 6). When

stimulation was persistently and adequately applied, varying degrees of local disturbances were noted, but the amount of reaction or destruction did not correlate with the development of gastrointestinal disturbances. Commonly, a thin zone of fibroblastic proliferation and gliosis was present around the active portion of the electrode, particularly when it approximated a pial surface (Fig. 6; Monkeys 40 and 45), but the animal in which such change was most extensive (Fig. 6; Monkey 45) displayed a normal stomach at autopsy. Moreover, Monkey 44 showed fairly extensive thrombotic change in the periventricular region, yet did not develop focal abnormality in the stomach.

When recordings were made from the implanted electrodes on a Grass amplifier and inkwriter, a normal pattern of electrical activity was exhibited.

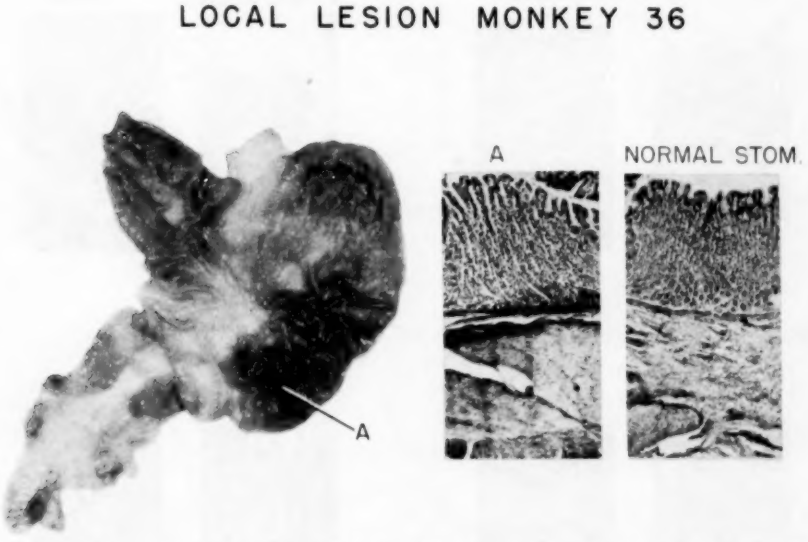

Fig. 2.—Photograph shows the stomach containing small lesion (*A*) in Monkey 36. The photomicrograph *A*, made from the site of the lesion, is seen to contrast markedly with the normal stomach.

Behavioral Observations.—Of the six animals which developed gastrointestinal lesions, three were male and three female. There was no correlation between the behavioral characteristics of the monkeys before stimulation and the development of gastrointestinal abnormalities. Of the six animals in which such disorders did result, three were considered initially to be placid and relatively friendly, while three were distinctly nervous and unfriendly. It was characteristic of all three friendly animals, however, that two to four weeks after stimulation began the behavior changed, antagonism, restlessness, and irritability being displayed. Such a change was not noted in those which did not receive appropriate excitation.

The immediate response of the animals during each stimulation period varied according to the location of the electrode, but there was usually a general similarity in the pattern of induced behavior. The animals appeared to be bewildered, occa-

sionally sitting cowed in a corner, or at other times restlessly and agitatedly pacing the cage. Yawning was common, as was barking. Apparently the animals associated the lead cables with the unusual state induced by the stimulus, as they would tug at the wires or chew on the leash frequently. Reactions generally associated with the expression of emotion were observed, these being characterized not only by subdued or agitated behavior, barking, yawning, pacing, and trembling, but also by dilatation of the pupils, ruffing of the hair, and an attitude of challenging aggression

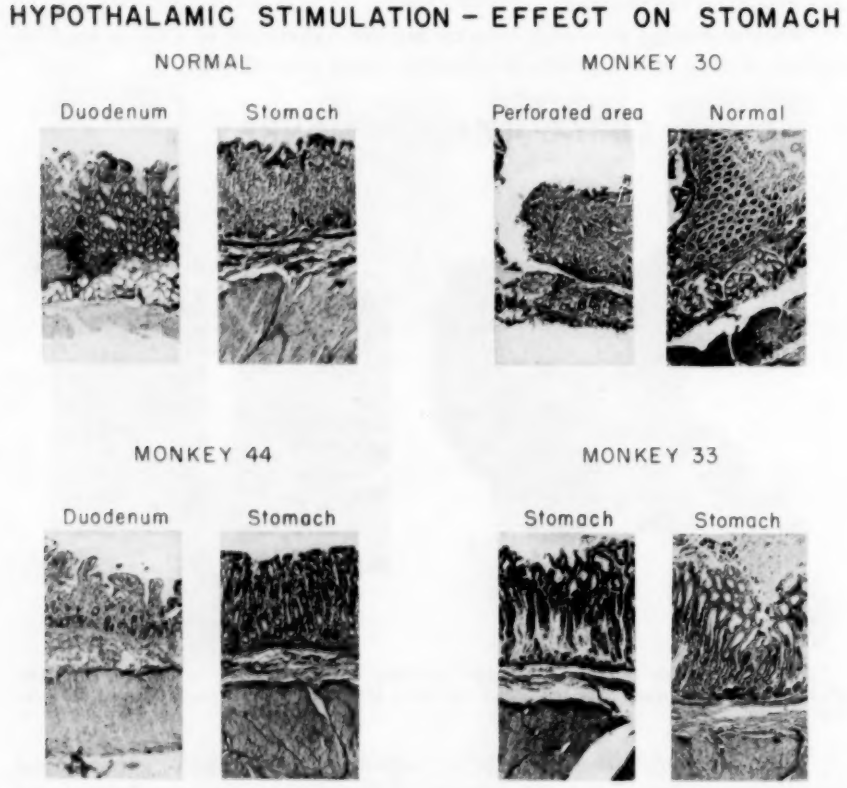

Fig. 3.—Photomicrographs demonstrate normal appearance of upper gastrointestinal tract (upper left) as contrasted with changes resulting from chronic hypothalamic stimulation. In Monkey 30, the perforated area (left of pair) shows replacement of Brunner's and mucosal glands by granulation tissue, while these structures appear much more normal in a segment of duodenum 1 cm. away. In Monkeys 44 and 33, which showed diffuse gastrointestinal changes, mucosal atrophy, fragmentation and distention of glands, and superficial erosion can be seen.

or impelling escape. The state of attentive adaptability was rarely altered, the animals apparently being entirely capable of appropriate action, such as grasping the leash or bits of food, following the examiner with its eyes, etc. Occasionally behavioral confusion was suggested by the actions exhibited, and infrequently, with higher voltages, a generalized seizure occurred. There was a tendency for animals stim-

ulated by more anteriorly situated electrodes to appear subdued, as opposed to more agitated expressions excited by posterior stimulations, but the distinction was not great. The behavior of individual animals to repeated stimulation periods was characteristically predictable, however, and this pattern of response persisted usually throughout the duration of the experiment.

The general health and nutritional state remained stable in all animals throughout the test period except for Monkey 30, which became critically ill (perforated duodenal ulcer) and was killed on the 30th day. There was no variation in appetite

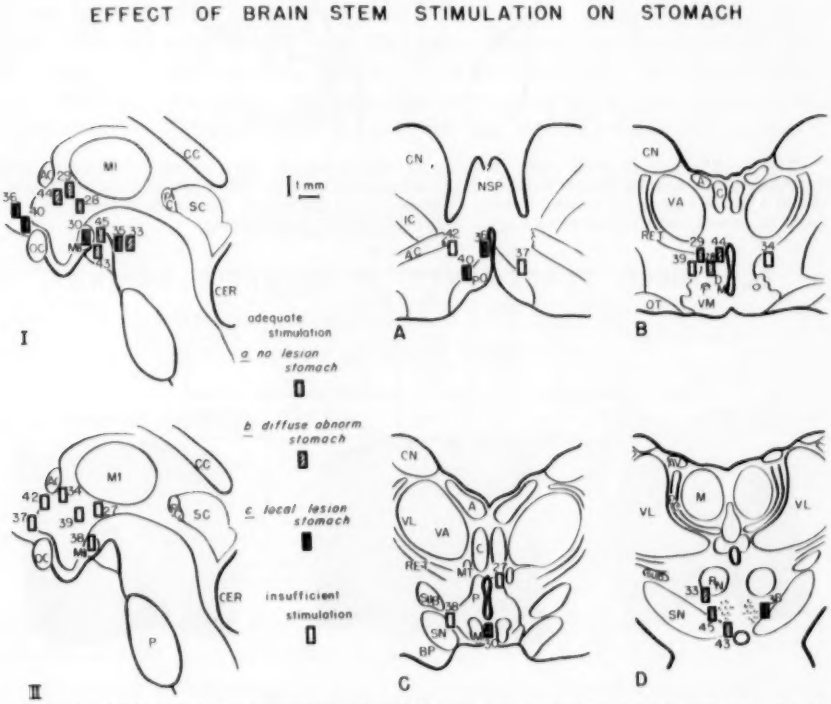

Fig. 4.—Midsagittal reconstructions (*I* and *II*) and cross sections (*A* through *D*) of brain stem of monkey show location of electrode placements. *I* denotes placements in animals which received adequate stimulation, while *II* denotes placements in insufficiently stimulated preparations. Note medial location of stimulation sites which were associated with focal lesions (solid bars) or diffuse abnormalities (hatched bars). Abbreviations: *A*, *AV*, *C*, *M*, *PC*, *RET*, *VA*, *VL*, *VM*, all thalamic nuclei; *AC*, anterior commissure; *BP*, brachium pontis; *CC*, corpus callosum; *CN*, caudate nucleus; *CER*, cerebellum; *F*, fornix; *IC*, internal capsule; *MI*, massa intermedia; *NSP*, nuclei of septum pellucidum; *OC*, optic chiasm; *OT*, optic tract; *P*, pons (*II*); *RN*, red nucleus; *SC*, superior colliculus; *SN*, substantia nigra; *SUB*, subthalamus.

Abbreviations for hypothalamic nuclei: *DM*, dorsomedial; *M*, mammillary body; *P*, paraventricular; *PO*, preoptic; *VM*, ventromedial.

In *D* "36" is incorrect; it should be "35."

observed in the adequately and in the inadequately stimulated group. Body weight was unusually stable, weight gain and weight loss being about evenly divided in monkeys which developed lesions and those which did not (Table 1). There was a tendency, in fact, for lesion animals to show more increase in weight than for all others.

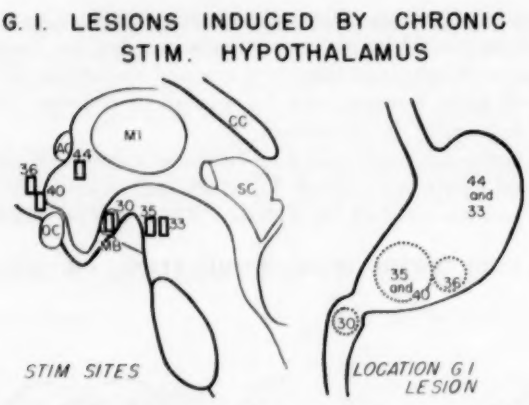

Fig. 5.—Diagram of brain stem (midsagittal reconstruction, left) contains stimulation sites (open bars) in animals which developed gastrointestinal lesions. Diagram of stomach (right) shows relative location of lesions induced in stomach and duodenum. Numbers in both diagrams refer to experiment number of monkey. Abbreviations as in Figure 4.

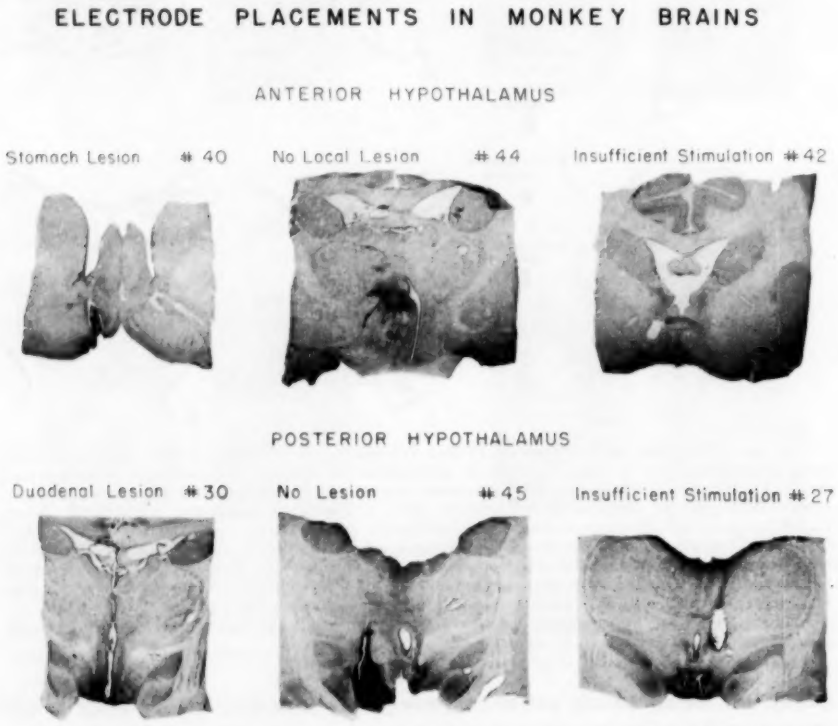

Fig. 6.—Photomicrographs of cross sections of the brain stem in monkeys demonstrate that residence of electrode (right-hand vertical pair) or induced destruction in brain (middle vertical pair) were not responsible for the production of gastrointestinal lesions. This result was obtained only when adequate stimulation was applied to an appropriate region in the hypothalamus (left-hand vertical pair).

Experimental Analyses.—The pH values noted on testing gastric samples of test animals before chronic stimulation, and again five weeks after it had begun, are reported in Table 2. Findings of the initial examination in the group of animals which later received insufficient stimulation were very similar to those of the test group, so that no distinguishing alteration of the gastric analysis existed from which it was possible to predict whether or not a lesion would develop. Five weeks after the beginning of chronic stimulation, however, such a distinction was suggested as, almost uniformly, both high and low pH's were depressed further in lesion than in nonlesion animals (Table 2).

The incidence with which occult blood was discovered in the stools of animals which developed lesions in the upper gastrointestinal tract was almost double that of nonlesion or insufficiently stimulated controls. Ordinarily, the first bleeding occurred 16 to 31 days after beginning of the experiment but did not appear in one animal until the 50th day. There was a slight but definite tendency for monkeys

TABLE 2.—*Results of Gastric Analysis before Chronic Stimulation and Five Weeks Later**

	ANIMAL	pH OF GASTRIC CONTENTS BEFORE AND AFTER CHRONIC STIM. OF BRAIN. BEFORE STIM. HIGH pH	BEFORE STIM. LOW pH	AFTER STIM. HIGH pH	AFTER STIM. LOW pH
FOCAL LESION	30P	5.8	2.6	4.0	2.8
	35A	6.0	3.8	2.8	1.8
	36A	3.3	2.1	4.3	2.2
	40A	7.2	5.6	3.2	2.3
DIFFUSE LESION	33P	7.4	3.2	6.2	2.8
	44P			4.2	2.1
NO LESION	28P	6.1	3.6	7.2	3.8
	29A	7.2	6.2	6.9	4.8
	43P	7.4	2.0	4.2	3.3
	45P	6.4	5.8	4.2	1.5

* Note that no consistent difference between lesion and nonlesion animals occurred before stimulation either at the extremes or in the range of pH values, while after stimulation a relative hyperacidity existed in monkeys which developed gastrointestinal abnormalities.

with posteriorly oriented electrodes (all groups) to show evidence of more frequent bleeding than for those with anterior placements.

Microscopic Changes in the Upper Gastrointestinal Tract.—MONKEY 30.—This animal was found to have an acute 5 mm. perforation in the anterior wall of the first portion of the duodenum, with local fibrinous adhesions and evidence of spreading peritonitis. Microscopically, the area surrounding the perforation showed almost complete absence of mucosal and Brunner's glands, these structures being replaced by a loose network of granulation tissue. The muscularis mucosa was fragmented and the muscular layers were edematous (Fig. 3).

MONKEYS 35 AND 40.—The gastric lesions exhibited grossly and microscopically by these animals were essentially identical (Fig. 1). The periphery of the lesion, microscopically, showed decrease in number, but dilatation, of glands, with increased numbers of lymphocytes in the mucosa. More centrally, the mucosal glands became severely fragmented, their lining cells showing evidence of necrotic change, and the entire thickness of the wall was intensely edematous. The mucosa of the central portion of the lesion was completely necrotic, outer layers having sloughed, and the muscularis mucosa was degenerate and fragmented. The changes in Monkey 35

appeared the older, as here the intense edema of the submucosa was replaced by dense strands of connective tissue, within which there was some, but surprisingly little, evidence of inflammatory reaction.

MONKEY 36.—The characteristic change noted in the region of the stomach containing the lesion was the friable, fragmented appearance of the mucosal glands, the apparent sloughing of their lining cells, and the atrophy of the submucosa (Fig. 2).

MONKEYS 33 AND 44.—Abnormalities were patchy in the upper gastrointestinal tracts of these animals, some areas appearing relatively normal, but the greater extent being distinctly pathological. Characteristically, there was seen atrophy and dilatation of the mucosal glands, with evidence of increased secretion of mucus (Fig. 3). The muscularis mucosa and submucosa were thinned and atrophic also.

Summary.—The striking features common to these lesions were edema, atrophy, and necrosis, evidence of inflammation or hemorrhage being minimal. Vascular changes were noted, but, as they were extremely complex, they will be reported at a later time. Evidence of thrombosis in small arterioles and venules was seen, and undoubtedly alterations in blood supply contributed greatly to the micropathology exhibited.

COMMENT

The monkey was selected as the animal of choice for these experiments for a number of reasons: It had been employed by us for other analyses involving investigations of (1) artificially induced stress, (2) the production of acute gastrointestinal disturbances by means of focal destruction in the diencephalon, and (3) mechanisms concerning neural influences upon the secretion of HCl by the stomach. Because of our familiarity with the reactions of monkeys to such experimental conditions, all appropriate to the problem at hand, it was deemed advisable to expand the investigation within the same species. Moreover, being a primate, the monkey would be expected to supply data more comparable to clinical observation than would other species more commonly investigated. Finally, focal lesions of the stomach are uncommon in Macacus mulattus; hence, their production would have added significance.

Experimental methods employed in the past to study the etiology of peptic ulcer have utilized, generally, one of three techniques, namely, (*a*) the application of local trauma to the alimentary tract, (*b*) introduction of systemic factors which act focally upon the stomach, and (*c*) alteration by operative intervention of normal gradients of gastrointestinal function.[4] Focal changes commonly induced by experiments patterned after types *a* and *b*, as outlined above, are frequently acute or transient, healing spontaneously upon removal of the noxious stimulus, or are preterminal. Etiological factors concerning lesions excited by operative alteration of intestinal gradients in animals are difficult to assess, as by such procedures conditions are imposed which deviate critically from those existing naturally. All of these measures have yielded much information pertinent to physiological alimentation and the induction of pathological change; yet, in most instances, they have established such abnormal states of nutrition or function that extrapolation of data so derived to the problem surrounding the spontaneous origin of focal lesions of the stomach and duodenum in man is extremely difficult.

The methods employed in these experiments were felt to avoid, in part at least, some of the problems raised above. It has been demonstrated previously, by acute

stimulation techniques, that physiological influences are exerted by hypothalamus upon the gastrointestinal tract.† Moreover, evidence was presented which suggested that these influences were subject to the laws of homeostasis and, abnormally excited, induced autonomic reactions characterizing the stressed state.‡ Chronic excitation of such existing mechanisms, therefore, active in normal visceral function but susceptible to excessive environmental challenge, would appear to present more valid conditions for physiological analysis than the creation of unnatural anatomical or functional states.

The gastrointestinal lesions observed in these experiments undoubtedly resulted from stimulation applied to certain regions within the hypothalamus rather than from the presence of electrodes within the brain, excessive experimental handling of the animals, destructive processes in the diencephalon induced by stimulation, or disturbances in metabolism, nutrition, or other systemic factors. All animals were subjected to identical environmental conditions, and only those known to have received prolonged excitation in the medial hypothalamus exhibited pathological change in the upper alimentary tract.

Prolonged stimulation in or near the hypothalamus was the common etiological factor in all lesions induced in these experiments. A single area mediating these deleterious influences upon the stomach could not be assigned, however, as identical results were obtained when excitation was applied to anterior as well as to posterior hypothalamic regions. Yet, the entire hypothalamus cannot be considered equipotential in its ability to excite gastric lesions, as stimulation of at least four points in it failed to elicit this response.

The possibility that different mechanisms, emanating separately from excitation of either anterior or posterior hypothalamic nuclei, were responsible for the production of these lesions requires consideration. Certainly, hypothalamic influences exciting hydrochloric acid secretion by the stomach are conducted by divergent routes, those from the preoptic area coursing through the vagus nerves, and others from the mammillary region by way of the pituitary-adrenal axis.[1] Moreover, acute gastric lesions, precipitated by localized destructions of anterior and of posterior portions of the hypothalamus, differ widely in their appearance, being predominantly hemorrhagic in the former instance and purely erosive in the latter.[3] Perhaps factors of chronicity imposed upon each of these nascent lesion types—erosive or hemorrhagic—by the stomach ultimately render them identical in appearance regardless of their mode of origin.

A third, and more likely, explanation for the genesis of these lesions is that the activation of each effective stimulating point excited at a different level the same complex combination of visceral effects necessary to create the rather precise conditions which resulted in focal tissue breakdown. Observations on these animals indicated that the disturbances in gastrointestinal function induced included alterations in blood flow and in secretion. Moreover, it has been demonstrated that changes in motility are easily excited by hypothalamic stimulation,§ and the gross appearance of the stomachs of our animals at autopsy clearly showed abnormal atonicity. The indications are, therefore, that effective stimulation sites in the hypothalamus were

† References 2, 5, and 6.
‡ References 3 and 7.
§ References 5 and 8.

so situated as to induce alteration in secretion, vascular supply, and motility in the stomach, and that these specific changes induced were all necessary for the ultimate development of focal lesions.

The location of effective stimulation sites in our animals suggests that structures conveying the mechanism necessary to excite these visceral changes course in the midline from preoptic to postmammillary regions at least. There is evidence that this hypothalamic segment represents a funneling of diverse visceral influences from widespread cerebral and brain stem sources, rendering them juxtaposed and excitable to a relatively small stimulation source.

Evidence concerning the nature and course of these influences, while fragmentary, is accumulating rapidly. Afferent pathways have been demonstrated from the splanchnic system to the region of the ventroposterolateral nucleus of the thalamus by Patton and Amassian [9] and from the vagus nerve to the orbital surface of the frontal lobe by Bailey and Bremer.[10] Starzl, Taylor, and Magoun [11] have described ascending connections between the central brain stem and the hypothalamus, as well as between central thalamic nuclei and cortical regions now known to mediate visceral influences.

Cortical areas which upon stimulation alter function of the upper gastrointestinal tract exist in rather widely dispersed fashion. Most extensively investigated in this regard has been gastric motility. Changes in contractility and tonus have been described following stimulation of discrete areas located in the orbital,‖ temporal,¶ and cingulate # regions. Moreover, Eliasson has described similar alterations of motility from excitation of the sensorimotor, frontal convexity, and parietal areas.[15]

Comparable observations have been made on the effects of cortical stimulation upon secretion and upon vasculature of the stomach. Davey, Kaada, and Fulton have noted increases in gastric juice, hydrochloric acid, and pepsin following excitation of Area 8,[16] and Eliasson, Lindgren, and Uvnäs observed vasodilatation in the stomach upon stimulation of the sensorimotor cortex.[17]

Whether or not these widely dispersed cortical areas exert their full effect upon the stomach through the hypothalamus is not entirely clear, although evidence suggests that the major portion of their influence is so conducted. Babkin and Kite [18] observed an increase in the rate of gastric contraction upon ablation of the cingulate gyrus in dogs, which effect was enhanced by mesencephalic section. Such section did not, however, enhance hypermotility induced by hypothalamic ablation. Moreover, Eliasson,[15] in tracing pathways from areas of cortex in parietal, orbital, frontal, and cingulate regions which were effective in altering motility, found them to course through the preoptic region, apparently en route to the hypothalamus.

Many observers have described the immediate effects upon the stomach of stimulation applied directly to the hypothalamus. Information concerning alterations in motility—both augmentation and inhibition—have been repeatedly summarized and expanded * since the earlier report of Beattie and Sheehan.[5] Marked alterations in blood supply to the stomach † and gastric secretory activity [1] have been shown to follow such stimulation.

‖ References 12 through 15.
¶ References 14 and 15.
# References 13 through 15.
* References 6, 8, and 15.
† References 6, 8, and 19.

That pathways conducting these influences upon function and dysfunction of the stomach and other visceral structures course through the brain stem,‡ vagus nerves, and sympathetic outflow § is clearly established. Moreover, an additional pathway has been described whereby the hypothalamus can influence function of the stomach. It has been demonstrated that the posterior hypothalamus, when excited to action by humoral [23] or electrical [7] methods, induces a state characteristic of "stress," one manifestation of which is an outpouring of hydrochloric acid by the stomach. Recently, Baker and Abrams [24] have shown experimentally that the elimination of this system by hypophysectomy produces profound and permanent changes in the secretory capacity of the stomach.

The lesions produced in the animals studied in the present experiments have not been called true ulcers, although certainly the similarity in their location, genesis, and appearance with clinical peptic ulceration is very striking. They were focally located in the prepyloric and postpyloric regions, contained necrotic centers, which even perforated in one instance, and developed progressively in response to situations of simulated stress. That chronic inflammation was poorly developed in them could indicate that a sufficient time for its development had not elapsed, and, judging from the microscopic appearance of the lesions, such reactive change would have been expected had the experiments been carried on longer.

It is evident, from the data reported, that development of visceral changes required excitation of appropriate regions in the hypothalamus for an appreciably long period of time. The first evidence that such lesions might be developing occurred in about 16 days, at which time occult blood was noted in the stools. After 25 days, however, one animal (Monkey 41), which might have been expected to develop a lesion from the reasonably close approximation of its stimulating electrode to that in others that did, had not developed one. The earliest verified lesion in this series appeared in 30 days (Monkey 30, perforated duodenum), at which time other subjects were beginning to display evidence of behavioral irritability and gastric hyperacidity. Other animals which were killed, after 55 to 71 days, showed local or diffuse changes in the stomach, which were distinct but appeared on microscopic examination to be still developing. It may be concluded, therefore, that the earliest manifestations of chronic gastric disease began with the third week of stimulation, but that fully developed lesions required 4 weeks in their genesis, some being delayed for as long as 10 weeks. Presumably, during this entire period the cessation of stimulation could have been attended by resorption and healing of the lesion or by ulceration and scarring, although in one instance the disease ran its complete course to perforation in 30 days.

The details concerning the origin and nature of the pathological processes involved in the genesis of lesions described must await further observation. It is probable, however, that a multiplicity of responsible events were precipitated, rather than that a single modality of function was disturbed. There was microscopic evidence, in fact, of vasomotor and of secretory disturbance, of mucosal atrophy, of diffuse edema and degeneration, and of inflammation. Doubtless, also, disturbances of motility and tonus were present. It is probable that these manifold, deleterious

‡ References 18, 20, and 21.

§ References 1, 2, 8, 14, 15, and 22.

influences, experimentally initiated by hypothalamic stimulation and mediated by way of the autonomic and endocrine systems, are comparable to similar events which may occur as a response to stress in higher orders.

Reference was made earlier to the dangers involved in making extrapolations from animal to man, particularly concerning disorders which have been called "psychosomatic." Evidence has been presented here, however, that a condition can be induced in monkeys which is strikingly similar, in many ways, to one observed commonly in the clinical experience of every physician. This latter disorder has been imputed, at least partially, to the physical and emotional stresses to which modern man is subjected. That observed in the monkey was induced by experiments designed to simulate the neural excitation induced by such stresses. As the matter cannot be explored directly in clinical practice, perhaps further evaluation of experimental data may lead to better understanding and more effective treatment of a disease which ranks high in incidence and morbidity in social experience.

SUMMARY

Daily stimulation was applied to the hypothalamus and adjacent regions of the brain stem in 17 monkeys. Ten animals received sufficient stimulation (30 to 74 days) to be considered as the test group, the remaining 7 serving as controls.

In the test group, six animals developed pathological changes in the upper gastrointestinal tract; four showed focal prepyloric or postpyloric lesions, and two exhibited diffuse gastric changes. The stimulation sites in these animals were found to be situated in the medial diencephalic axis from preoptic to postmammillary regions. Excitation to the remaining four animals had been applied to regions near, but outside, this zone.

During the period of stimulation, animals which ultimately developed lesions behaved in an irritable fashion and exhibited hyperacidity of gastric secretions, as well as occult blood in the stools.

The probable mechanisms activated by stimulation in these experiments are described.

Points of similarity between the disorder induced in these animals and the clinical manifestations of peptic ulceration in man are discussed.

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CENTERING OF EYES

A Patterned Eye Movement

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IN A STUDY of patterns of eye movements obtained on electric stimulation of the brain stem, cerebellum, and cerebrum in the monkey, there was one type of binocular action which has seldom been mentioned in the conventional classification of eye movements. This was a centering of the eyes to the midposition regardless of the location of the globes prior to the stimulation. Magoun, in his earlier investigations of the brain stem, recorded such eye movements in his protocols, but he did not attach particular significance to them. In our preliminary note, made in 1948, we called this ocular movement "the midposition phenomenon." [1] The same phenomenon had previously been observed by others who investigated cerebral function. In 1888 Beevor and Horsley [2] and in 1890 Mott and Schaefer [3] noted this centering in their observations on stimulation of the frontal lobe. Brown [4] interpreted this midpositioning as "the orientation of the optical axes reflex," while Smith * named it "the awakening response." These terms are more explanatory than descriptive in their meanings. Since conjectural explanations may obscure the existing problem, we prefer to use the descriptive term midpositioning phenomenon, or centering of the eyes.

As noted above, centering of the eyes occurs regardless of the position of the globes prior to the stimulation. With the eyes laterally or vertically deviated in a convergent, divergent, or skew position, application of the stimulus brings the globes to the midposition. Unless succeeded by a specific ocular deviation, the eyes remain in the midposition as long as the stimulus is continued. Moreover, if the eyes happen to be in the midposition, then no movement occurs on stimulation. The object of the present experiments is to ascertain (1) from which regions of the brain stem † the midpositioning phenomenon could be obtained on electric stimulation; (2) whether it is one manifestation or a more generalized response, such as an autonomic (sympathetic) effect or part of a more diffuse somatic pattern; (3) the degree to which

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Work aided (in part) by Grant #B-294 from the United States Public Health Service.

* References 5 and 6.

† In these experiments we also studied the effects of electric stimulation of parts of the cerebellum and parts of the cerebrum. Since these structures have not been completely explored or studied from the standpoint of eye centering, they will not be included in this communication.

it may be interpreted as a part of an "alerting" or "awakening" reaction, and (4) whether the midpositioning is a patterned ocular movement per se, analogous to a lateral or vertical ocular deviation.

MATERIAL AND METHOD

Twenty-three cats and 58 monkeys, including 57 Macacus mulattus and 1 M. cynomolgus, were studied with the Horsley-Clarke stereotaxic technique, as described in our previous communication.[7]

The animals were anesthetized with intravenous pentobarbital (Nembutal) sodium, 30 mg. per kilogram of body weight. In a few experiments light ether anesthesia was used. Stimulation of the cerebellum, diencephalon, and brain stem was carried out in the vertical, diagonal, and horizontal planes with a bipolar electrode at 0.5 to 1 mm. intervals. A pulsating, spike-shaped current was supplied through a Dumont variable frequency stimulator, the frequency being kept constant at 250 cps. In more recent experiments square-wave stimulation at 250 cps was used. Every point explored was tested repeatedly with varying voltages. The response obtained with the minimal voltage, from 0.8 to 4.5 volts on the Dumont and 1 to 3 volts on the square-wave stimulator, was considered as "primary" at the point of stimulation.

In all, 69 tracts, including 35 horizontal, 26 vertical and 8 diagonal, through the cerebellum, the diencephalon, and the brain stem of the 23 experimental cats, and 260 tracts, including 197 vertical, 60 horizontal, and 3 diagonal, through the same structures of the 58 monkeys were explored. The area of the brain stem stimulated extended from the diencephalon and pretectal region to the caudal portions of the medulla, from the most dorsal to the most ventral portions of the entire brain stem, and laterally for 6 to 7 mm. from the midline. In recent brain stem stimulation experiments simultaneous electroencephalographic recordings were made. The instrument used was a Medcraft Model D-8-channel electroencephalograph. Recordings were made through phonograph needle electrodes implanted in the skull, resting on the dura, over the frontal, parietal, and occipital areas, and one at the midline over the vertex.

Anatomic studies were made at scheduled intervals. The animals were killed under general anesthesia. With the aid of the Horsley-Clarke instrument four guide wires were inserted vertically through the brain. Two were 10 mm. in front of, and two behind, the vertical zero plane, 5 mm. lateral to the midline. Two horizontal wires were inserted 5 mm. from the midline, one at the interauricular, or zero horizontal, plane, and the other 10 mm. below this plane. The cerebrum, cerebellum, brain stem, and a portion of the upper cervical cord were then removed en masse. The specimen, including the inserted guide wires, was fixed in 20% formaldehyde solution. After fixation in formalin, a block of tissue, which included the whole brain stem, the central part of the cerebellum, and a small portion of the cerebrum, was cut along the anterior and the posterior guide wires. The block was embedded in celloidin for serial sections. Each section was 50 μ in thickness, and each 10th and 11th section was stained by the Weil and Nissl methods, respectively. The amount of tissue shrinkage caused by the process of fixation was calculated from the distance between the midline and the two holes made by the horizontal wires at H-0 and H-10, as well as between the two pairs of vertical wires. Each explored point from which response had been obtained was plotted according to the coordinates of the Horsley-Clarke instrument.

RESULTS

Under general anesthesia and before the application of the electrical stimulus, the eyes of the experimental animal might be seen in any position, i. e., deviating to one side, upward or downward or in a skew pattern, or showing a slow pendulous movement. Upon stimulation at a reactive point, the eyes moved to the midposition. The response was almost always binocular. However, there were monocular centerings which were ipsilateral or contralateral to the side of stimulation. The motion of the eyes during the midpositioning was relatively slow and rolling. This was in contrast to the sharp, rapid, snappy individual ocular displacement that was obtained by stimulation of the oculomotor, trochlear, or abducens cranial nerves, rootlets, or nuclei.

Anatomical Representation of the Midpositioning in the Brain Stem.—(*a*) Midpositioning of Eyes: The midpositioning phenomenon was obtained with a low-voltage stimulus from many areas close to the midline or in the paramedian zone (Table 1 and Figure, upper) and from regions in the diencephalon, mesencephalon, pons, and medulla, as well as the cerebellar central nodule. It should be stated that it is often difficult to assign the effects of stimulation to a particular anatomic locus in the brain stem because of the juxtaposition of fiber pathways and of the reticular substance which forms the matrix of the stem. Taking these anatomic facts into consideration, it was noted that electrical stimulation with minimal voltages produced binocular midpositioning without other visible motor phenomena.

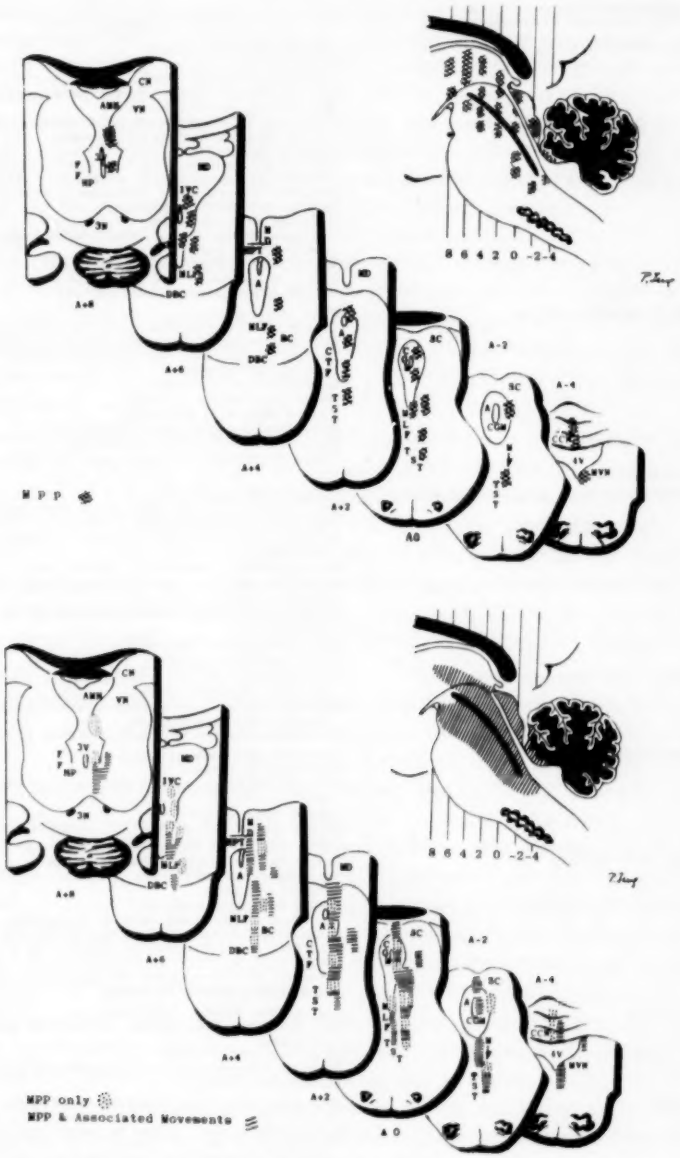
TABLE 1.—*Midpositioning Phenomenon and Its Related Anatomical Structures of Cerebellum and Brain Stem in Monkey*

Observation	Anatomical Structures
Midpositioning phenomenon with no associated movement	Medial thalamus, paraventricular region
	Ventromedial thalamic nucleus
	Medial dorsal thalamic nucleus
	Tract of Vicq d'Azyr, lower part
	Fibers to interventricular commissure
	Interventricular commissure
	Central gray matter, 1 mm. dorsal to III nerve nucleus
	Central gray matter
	Tectotegmental and habenulopeduncular fibers
	Red nucleus
	Posterior commissure
	Lateral fibers of posterior commissure in pretectal region
	Lateral border of central tegmental fasciculus and adjacent reticular substance
	Decussation of brachium conjunctivum
	Reticular substance, ventral portion of; pons; longitudinal fasciculus near rootlets of IV nerve nucleus
	Brachium conjunctivum
	Tecto-olivary tract and adjacent reticular substance
	Tectospinal tract
	Medial vestibular nucleus
	Cerebellar central nodule, midline and areas close to midline

Increasing the strength of the stimulus usually brought out one or more of the associated manifestations as listed in Table 2. These secondary actions depended on the location of the stimulation. In many instances, however, these associated movements could be produced even with small voltages. Although centering of the eyes could be obtained as an isolated response from some regions, the following manifestations were obtained in conjunction with the midpositioning when greater voltages were used in different regions of the brain stem.

(*b*) Midpositioning and Pupillary Dilatation: Dilatation of the pupil was the most commonly observed manifestation in association with the eye centering under these particular conditions of testing.‡ This pupillary dilatation was usually bilateral. Occasionally it was monocular, either homolateral or contralateral. When the response was binocular, both pupils were usually dilated equally. Nevertheless, on many occasions one pupil dilated more than the other, either homolaterally or contralaterally to the side of stimulation.

‡ This does not mean that other associated phenomena not apparent to us under these conditions of testing were less frequent.



(Upper) Diagram of transversal sections of the diencephalon and brain stem shows midpositioning phenomenon with most reactive areas (cross hatched).

(Lower) Diagram of transversal sections of the diencephalon and brain stem shows midpositioning phenomenon and its associated responses (cross hatched). Dots indicate the most reactive areas of midpositioning phenomenon without any associated response.

TABLE 2.—*Midpositioning Phenomenon: Its Associated Ocular and Body Movements and Their Related Anatomical Structures of Cerebrum and Brain Stem in Monkey*

Associated Movements with Midpositioning Phenomenon	Anatomical Structures
Pupillary dilatation, O. U.	Cerebellar central nodule Field of Forel Habenulopeduncular tract Inferior edge of bundle of Vicq d'Azyr Red nucleus, ventromedial part Fibers of dorsal tegmental decussation Nucleus dorsalis medialis of thalamus Superior colliculus Central gray matter, close to III nerve nucleus Posterior commissure near central gray matter Brachium conjunctivum, including decussation Inferior colliculus, medial part Reticular formation, close to decussation of brachium conjunctivum, medial longitudinal fasciculus, or tecto-olivary tract Medial longitudinal fasciculus of pons Fibers of central tegmental fasciculus Central gray matter, lateral part
Widening of palpebral fissure	Field of Forel Interventricular commissure, lateral and lower part Superior colliculus, close to central gray matter Central gray matter, near III nerve nucleus Posterior commissure Cerebellar central nodule Reticular substance of pons Central tegmental fasciculus Reticulorubro-olivary tract, lateral part Decussation of brachium conjunctivum Tegmental decussation, near III nerve fibers
Other ocular movements	
1. Contralateral ocular conjugate deviation	Medial vestibular nucleus Posterior commissure, near central gray matter Fibers of central tegmental fasciculus Reticular substance, lateral part of central tegmental fasciculus Interventricular commissure, lateral part
2. Ipsilateral ocular conjugate deviation	Reticular substance, near tectospinal tract Cerebellar central nodule Central gray matter and ventral border of brachium conjunctivum Central tegmental fasciculus Medial vestibular nucleus
3. Upward ocular conjugate deviation	Decussation of brachium conjunctivum, lower part at junction of base of pons Lateral part of reticulorubro-olivary tract and neighboring reticular substance Reticular substance at junction of base of pons
Pupillary constriction	Interventricular commissure Posterior commissure Superior colliculus, medial part close to central gray matter Central gray matter Medial border of nucleus of posterior commissure, close to central gray matter
Integrated facial patterns	Decussation of brachium conjunctivum Reticular substance of pons Genu of VII nerve Medial vestibular nucleus Brachium conjunctivum close to decussation Reticular substance and junction of tecto-olivary tract Central tegmental fasciculus and lateral part of VII nerve Reticular substance close to tectospinal tract and medial longitudinal fasciculus
Jaw movements	Central gray matter, lower part Reticular substance lateral to medial longitudinal fasciculus Cerebellar central nodule Reticular substance close to tecto-olivary tract Tecto-olivary tract
Vocalization	Deep stratum of rostral portion of inferior colliculus, 2 mm. from lateral border of central gray matter Reticular substance adjacent to ventral portion of central gray matter and portion of central gray matter close to aqueduct under inferior colliculus
Body movements	Lower part of central gray matter Decussation of brachium conjunctivum Red nucleus Central tegmental fasciculus Reticular substance, junction of base of pons Cerebellar central nodule Field of Forel, fibers of dorsal tegmental decussation, ventromedial border of red nucleus Tegmental decussation, close to III nerve fibers Tectospinal tract, lateral part Reticular substance, lateral border of reticulorubro-olivary tract
Changes in respiration	Central gray matter Deep stratum of superior colliculi close to central gray matter Reticular substance of pons, lower part

In order to determine whether the midpositioning and the mydriatic effects were each due to sympathetic excitation, the following experiments were carried out: In four monkeys unilateral section of the cervical sympathetic trunk, including excision of the superior cervical ganglion, was done prior to the electrical stimulation of the diencephalon and brain stem. In each of these animals there developed a Horner syndrome on the sympathectomized side. Stimulation of the midpositioning reactive areas with minimal voltage then produced bilateral centering of eyes but no pupillary dilatation on the sympathectomized side; the pupil on the intact side responded accordingly with a good dilatation. In some instances stimulation in areas close to the oculomotor nucleus resulted in a midpositioning of both eyes, with a slight to moderate dilatation of the pupil on the sympathectomized side, as well as a conspicuous dilatation on the intact side. In the cat, the pupillary dilatation on the sympathectomized side was even more pronounced. The dilatation on the side with the Horner syndrome has been interpreted as a result of inhibition by the oculomotor system.§

Binocular pupillary dilatation as a change associated with the midpositioning was elicited from a wide area in the diencephalon and the brain stem. It also appeared on stimulation of the cerebellar central nodule, the nucleus dorsalis medialis, the tegmental field of Forel, the habenulopeduncular tract, the inferior edge of the bundle of Vicq d'Azyr, the ventromedial part of the red nucleus, the fibers of the dorsal tegmental decussation, the periaqueductal gray matter, the posterior commissure, the fibers of the brachium conjunctivum emerging into the decussation, the decussation of the brachium, the reticular formation, the medial longitudinal fasciculus, and the central tegmental fasciculus (Table 2).

(*c*) Midpositioning and Widening of the Palpebral Fissure: With the midpositioning and pupillary dilatation there was often a widening of the palpebral fissure in both eyes. This was found in many, but not all, reactive points. It is significant that on stimulation of the midpositioning reactive area in the brain stem there occurred a widening of the palpebral fissure, even on the side in which the cervical sympathetic trunk and ganglia were excised. In fact, this widening of the fissure occurred in monkeys in which the ipsilateral facial nerve and cervical sympathetic trunk were both sectioned. This finding suggests that the widening of the palpebral fissure, as well as eye centering, was not mediated through the cervical sympathetic system. The enlargement of the palpebral fissure was either unilateral or bilateral, or one was wider than the other. The wider one occurred either ipsilateral or contralateral to the side of stimulation. As a rule, however, the widening of the palpebral fissures, together with the centering of eyes and the dilatation of the pupils, gave the animal a wide-awake appearance of staring and alertness. In the cat, there was also a retraction of the nictitating membranes, which, of course, is a sympathetic effect. The bilateral widening of the palpebral fissures was obtained from the excitation of the tegmental field of Forel, the lateral and lower part of the interventricular commissure, the posterior commissure, the central gray matter, the central tegmental fasciculus, the decussation of the brachium conjunctivum, the tegmental decussation, the reticulorubro-olivary tract, and the reticular formation, as well as the cerebellar central nodule.

§ References 8, 9, and 10.

(*d*) Midpositioning and Other Ocular Movements: From the cranial nerve nuclei and their fibers and the medial longitudinal fasciculus, the midpositioning phenomenon was frequently masked or "overcome" by the response characteristic of stimulation of these particular structures. Thus, in the stimulation of the fourth nerve nucleus one obtained a contralateral intorsion of the globe and a centering in the ipsilateral eye. From the oculomotor nucleus and rootlets there was an internal upward or downward rotation of the homolateral eye and a centering in the contralateral eye. From the medial longitudinal fasciculus there was adduction of the contralateral and a midpositioning of the ipsilateral globe.[11]

The distinct contralateral conjugate deviation obtained from stimulation of the medial vestibular nucleus, central gray matter, interventricular commissure, junctional area of the reticular formation and the central tegmental fasciculus, and the posterior commissure adjacent to the central gray matter was usually preceded by a slower, but conspicuous, midpositioning of the eyes.

Ipsilateral conjugate deviations of eyes were also preceded by the midpositioning phenomenon. This was observed on stimulating points in the reticular formation near the tectospinal tract, the central gray matter, the ventral border of the brachium conjunctivum, the central tegmental fasciculus, the medial vestibular nucleus, and the cerebellar central nodule. As already noted, this deviation was often preceded by an obvious midpositioning. In some instances the midpositioning phenomenon appeared to compete with a conjugate eye movement, and here a transient horizontal nystagmus resulted. This could be reproduced on repeated occasions.

The midpositioning phenomenon was observed in stimulations which resulted in upward or in downward gaze. Stimulation of foci in the lower portion of the decussation of the brachium conjunctivum, the reticular formation at the upper border of the base of the pons, the lateral part of the reticulorubro-olivary tract, and its adjacent reticular formation produced an upward movement of the eyes. Midpositioning was also noted prior to downward movements. In all of the instances in which midpositioning preceded ocular deviation in the horizontal or vertical plane there were no manifestations of sympathetic activity. In general there was no pupillary dilatation or widening of the palpebral fissure, unless very strong stimuli were used or the area stimulated was on the periphery of the area from which ocular deviation could be obtained. The significant finding was the centering of the eyes, as though they oriented themselves along optic axes prior to the particular conjugate deviation.

(*e*) Midpositioning and Pupillary Constriction: Stimulation in the region of the central gray matter, the posterior commissure, and the interventicular commissure of the diencephalon resulted in bilateral pupillary constriction and simultaneous centering of the eyes. In regions near the rostral end of the oculomotor nucleus there was ipsilateral pupillary constriction, contralateral pupillary dilatation, and bilateral midpositioning. From the interventricular commissure and the habenulopeduncular tract, there was an initial pupillary constriction followed by pupillary dilatation. In one monkey, on stimulation of the central gray matter close and lateral to the aqueduct, bilateral protrusion of the irises and midpositioning were observed.

(*f*) Midpositioning and Integrated Facial Patterns: The centering of eyes was also noted in evoked complex face movements.‖ By changing the stimulating cur-

‖ References 12 and 13.

rents, a wide variety of facial movements were observed with ocular midpositioning. These facial movements were more varied and complex in the monkey than in the cat. They occurred either unilaterally or bilaterally and involved either the whole or a part of the face. When bilateral, the movements suggested grimacing, snarling, pouting, and laughing-like expressions. The widening of the palpebral fissure associated with midpositioning was sometimes decreased by the antagonistic orbicularis oculi action (lid closure). These facial movements differed from those obtained on stimulation of the facial nucleus, rootlets, and nerve in that they were not tetanic, but smooth and life-like. Integrated facial movements were obtained from the stimulation of the reticular substance, the vicinity of the medial vestibular nuclei, the brachium conjunctivum and its decussation, the reticular formation close to the medial longitudinal fasciculus or adjacent to the tecto-olivary tract, as well as the tectospinal tract, and the central tegmental tract.

(*g*) Midpositioning and Jaw Movements: Movements of the jaw, slight closure or opening, were elicited in association with the midpositioning. These mandibular movements differed from those obtained by the direct stimulation of the fifth cranial nerve motor nucleus, its rootlets or nerve, or the mesencephalic rootlets of the same nerve, which produced quick and forceful movements of the mandible. The associated jaw movements with midpositioning were patterned and resembled very much the jaw dropping or closure when one is caught by surprise. The opening of the jaw was also seen in association with changes of respiration and vocalization. The jaw action was bilateral, slow, and weak.

These particular jaw movements were frequently obtained from stimulation of the lower portion of the central gray matter, the reticular formation neighboring the medial longitudinal fasciculus, or the tecto-olivary tract, and the cerebellar central nodule.

(*h*) Midpositioning and Vocalization: Eye centering was also associated with vocalization. This was obtained by stimulation of the deep stratum of the rostral portion of the inferior colliculus, 2 mm. from the lateral border of the central gray matter, the reticular formation adjacent to the ventral portion of the central gray matter, and the portion of the central gray matter close to the aqueduct at this level. Stimulation in this region produced an unsustained eye centering, which was then followed by a subsequent contralateral conjugate deviation. Vocalization and eye centering were also obtained on stimulation of the reticular formation between the lateral lemniscus, the brachium conjunctivum, and the tecto-olivary tract.

Midpositioning of eyes and vocalization from a complex pattern of movement which involves the extraocular, the facial (unilateral or bilateral contraction), the oronasopharyngeal (jaw opening, depression of tongue, flaring of the nostrils, elevation of the palate, and phonation), and the respiratory (rapid and deep respiration, contraction of the diaphragm) muscles.

(*i*) Midpositioning and Complex Body Movements: In addition to facial and jaw contractions, movements of the head, shoulders, trunk, arms, and legs were recorded with the midpositioning. The most complete pattern was best obtained from the region of the tectospinal tract and the vermis of the cerebellum. When the tectospinal tract was stimulated bilaterally by an electrode in the midline, a fused pattern of purposeful movement was obtained—the monkey leapt ahead or jumped back. With these movements of the body were facial expressions as if the animal

was snarling, with the ears flattened against the head. In many instances the head was seen thrusting forward, with the shoulders elevated, the forepaws flexed, and the hind limbs extended. The animal then appeared to be focusing its gaze as in acting against an assailant. At times the movement of the shoulder was only unilateral, and so, too, were the movements of the limbs. The contralateral limbs often flexed or extended at the large joints, or sometimes at the smaller joints of the hand and foot. The same point might give a forward or backward movement when stimulated at different times. Also, the flexion of a limb could be changed to extension by altering its position prior to stimulation.

Complex body movements and eye centering could also be obtained from the field of Forel, the lower part of the central gray matter, the region of the red nucleus, the tegmental decussation, the reticulorubro-olivary and their neighboring reticular formation, and the cerebellar central nodule.

(*j*) Midpositioning and Changes in Respiration: Frequently a change in respiration was noted in association with midpositioning of the eyes. There was either an inhibition at inspiration or at expiration or an increase in rate or depth of respiration. All of these changes were obtained from the stimulation of the various parts of the paramedian reticular formation at the level of the lower pons. Midpositioning and an increase of the respiratory rate were also elicited from the central gray matter, as well as from the deep stratum of the superior colliculi close to the central gray matter.

(*k*) Midpositioning and Electrical Phenomena: Electroencephalographic recordings from the frontal, central, and occipital regions disclosed two distinct types of change in association with the midpositioning, one a synchronous slow activity and the other a loss of activity. Stimulation of the cerebellar central nodule elicited midpositioning, but without any change in the electroencephalographic recordings. A detailed description of our electroencephalographic studies in concomitance with the midposition phenomenon has been reported in a separate article.[14] In brief, the principal findings were as follows: 1. The reactive areas in the brain stem which produced electrical changes in the cortex were mainly the median and paramedian zones of the midbrain and pons and upper medulla. 2. A unilateral stimulus in the brain stem produced a diffuse bilateral electrical change in the cortex, most marked in the frontal leads. 3. The electrical change in the cortex was either (*a*) loss of activity, a flattening of the record, or (*b*) a greater synchrony, slowing and symmetry of the record. 4. Either of these two types of response was obtained on stimulating the same focus of the brain stem in different monkeys. However, only one of these two types of response could be consistently obtained in the same animal. 5. The electroencephalographic changes were most frequently associated with centering of the eyes. At times, however, there was no apparent concomitant ocular centering. Conversely, there were several regions from which midpositioning of eyes occurred without simultaneous changes in the electroencephalographic rceording.

COMMENT

A possible explanation for midpositioning or centering of eyes is that it is part of an autonomic (sympathetic) effect. Certainly the occurrence of midpositioning with pupillary dilatation and widening of the palpebral fissures is suggestive of sympathetic activity, particularly since this pupillary dilatation is reduced by cervical

sympathectomy. It is significant, though, that such a sympathectomy does not abolish the centering of the eyes. Moreover, in some areas there resulted centering of the eyes without pupillary dilatation. These findings suggest, therefore, that sympathetic activity may accompany, but is not necessarily the basis of, eye centering, just as autonomic activity may be associated with many types of bodily reactions. The ocular midpositioning which may occur with pupillary dilatation and widened palpebral fissures may thus be conceived as part of a generalized alerting pattern—an integrated somatic and autonomic action.

This hypothesis is supported by the observations that stimulations with stronger current in certain regions of the brain stem brought out muscular actions of the face, neck, trunk, and limbs in integrated patterns suggestive of purposeful movements, such as aggressive or defensive activity. Not infrequently the experimental animal appeared as if it were thrusting the body forward as though attacking or reacting to an assailant, with the movement of either arm giving the impression of reaching or sparring. The associated complex movements of the face gave the impression of snarling or threatening with anger. The reactions obtained on electric stimulation of the brain stem simulated the behavior of an animal alerted to an abrupt change in its external environment calling for action. One of the many motor manifestations of this state of alertness might be midpositioning of the eyes. Ocular centering is a pattern of movement which participates in the activity of the total organism. The particular performance of the eyes varies with the environmental situation in which the animal might be.

Besides the observed eye centering and body movements, there are other changes which occur on stimulating the regions of the brain stem described. These changes may not be apparent on inspection of the animal. For instance, there may be sensory or visceral phenomena. There also may be changes which could be measured only electrically, namely, alterations in electroencephalographic recordings. It happened that many, but not all, of the reactive foci in the brain stem which produced midpositioning of the eyes also yielded alterations in electroencephalographic recordings.

In this paramedian area of the brain stem, Magoun [15] and Moruzzi and Magoun [16] demonstrated in cats, and later in monkeys, that the stimulation of the reticular formation and its relays produced a desynchronization of the electroencephalographic record. Their experiments were carried out on nonanesthetized animals in which the upper cervical cord was transected. They interpreted these changes as an arousal or waking reaction. They postulated an ascending reticular activating system which mediates this electroencephalographic change interpreted as wakefulness. A similar generalized acceleration of spontaneous electrocortical activity was observed by Jasper and his associates, in 1948,[17] from the stimulation of the periaqueductal portion of the midbrain, the posterior thalamus, and the massa intermedia of the thalamus. Ward, in 1949,[18] also obtained a prolonged generalized increase in both voltage and frequency of the electrical activity following stimulation of the bulbar reticular formation.

From the foregoing discussion it would seem that centering of the eyes obtained on electric stimulation of the brain stem is part of an alerting or waking pattern. This hypothesis tends to be supported by the concurrent autonomic, somatic, and, possibly, electroencephalographic changes assumed to be characteristic of an alerting situation

in an animal. However, we must not overlook other data in our experiments which do not support this hypothesis. For instance, there are regions in which electric stimulation produced only a centering of eyes. On the other hand, there are regions which yield somatic and electroencephalographic changes but without eye centering. While it may be true that midpositioning of the eyes is part of an alerting reaction, it does not exclude the possibility that such ocular movements may be a patterned action which may take place in other types of performance. It may be that centering of the eyes is a type of conjugate eye movement, just as is an ocular deviation to the right or the left or up or down. We happened to study the brain stem, and it is only because of recent studies by Magoun that the question of the alerting or waking pattern was raised. It must be borne in mind that centering of eyes may be observed in studies of the cerebrum. What we have observed in the brain stem experiments has also been found in stimulation of the cerebrum.¶ In our own experiments on the frontal lobe, occipital lobe, and posterior parietal lobe, we also found that unilateral stimulation resulted in a bilateral centering of eye movements.# Penfield,[19] in his studies of electric stimulation of the temporal lobe, describes a staring of the eyes as part of a petit mal seizure. The cerebral zones from which the midpositioning could be obtained are fairly widespread. There is no adequate proof that the eye effects elicited from the cerebrum are solely part of an alerting pattern. It may well be that eye centering is a patterned eye movement which may participate in a variety of performances. There is a possibility that in the normal waking state the globes are maintained in their vertical and horizontal axes by its operation. One may postulate a homeostatic or "cybernetic" action whereby visual stimuli set into motion a mechanism for the correction of deviation of eyes.

Pitts and McCulloch have suggested a mathematical model for "reflex" centering motions of the eyes, i. e., for the ocular movement which brings a bright target from the periphery of the field of vision into the fovea.[20] These authors take their clue from Apter's demonstration * of a sensory and motor map on the cat's superior colliculi. In Apter's work, stimulation of points of known position on the retina of the cat, with short flashes of light, led to the appearance of evoked potentials on the superior colliculi. The maximal potentials were found in collicular regions corresponding to the stimulated region of the retina, the upper field being medial on the colliculus, the lower field lateral. Correspondingly localized strychninization of collicular regions,[23] combined with diffuse illumination of the retina, led to eye movements in predictable directions. With strychnine on the medial aspect of the superior colliculus the cat looked up; with strychnine on the lateral region of the colliculus, the cat looked down.

On the basis of these findings, Pitts and McCulloch [20] proposed that the superior colliculus "computes . . . the lateral and vertical coordinates of the center . . . of the distribution of brightness referred to the point of fixation as origin, and supplies impulses at a rate proportional to these coordinates to the lateral and vertical eye-muscles in such a way that these then turn the visual axis toward the center." Elec-

¶ References 2, 3, and 4.

Further researches on electric stimulation of the cerebrum are now in progress with the purpose of determining all the cerebral areas from which eye centering could be elicited.

* References 21 and 22.

tronic analogues for such a mechanism based on the principle of the servomechanism or "negative feedback" (control of output by continual comparison with input) could easily be constructed.

The attributing of such characteristics to the superior colliculi is an extremely attractive theory. The more recent disclosures of direct connections between the occipital, as well as frontal, eye fields and the superior colliculi † provide further arguments in favor of the theory. By suggesting that the calcarine cortex might "map" in the colliculi as does the retina, Pitts and McCulloch [20] have opened the way for the assumption that corticofugal influences may enter into the total balance of excitation on the collicular surface. On this basis, one might be able to understand why partial destruction of the calcarine cortex or of frontal eye fields may lead to systematic ocular deviations; yet such deviations are usually transient.

If the centering of the globes is considered to be a pattern of normal ocular movement, the question arises as to how an irritative or paralytic phase of this midpositioning function would be manifested. The attacks of staring and eye centering which occur in petit mal may be considered as the irritative manifestation. Is there a paralytic manifestation? Is it possible to produce a paralysis of centering of eye movement by a lesion in the nervous system in the experimental animal, just as one can reproduce a paralysis of horizontal or vertical conjugate gaze? The answer is that we have not observed any one patient who had an isolated difficulty in centering of his eyes except when there happened to be a defect in one of the eye muscle functions. Paralysis of convergence might be an example, but it is doubtful whether one can interpret it as a paralysis of eye centering. Perhaps the ocular divergence or drifting one finds in a comatose patient or during anesthesia or the position the globes assume in sleep may be considered as examples of a lack of centering of the eyes. Another possible symptom of a lesion in the reactive area for eye centering in the brain stem might be nystagmus on forward gaze when the eyes are in midposition. Nystagmus on forward gaze may be noted in one or both eyes, and the jerks may occur in the horizontal or the vertical plane. This problem of nystagmus on forward gaze is still unsolved. There is very little theoretical information and there are few anatomical or experimental data on this subject. Little is known about the pathologic physiology of this condition, and since there have been very few clinicopathologic studies, it is difficult to correlate nystagmus on forward gaze with the anatomical areas which on stimulation bring about ocular midpositioning. It might be worth while to consider the hypothesis that in cases of nystagmus on forward gaze the lesion is in some region of the brain stem from which we get centering of eye movement. The interference may possibly be in an area through which fiber bundles conduct impulses for individual eye or binocular movements. This theoretical problem has heuristic value and requires experimental and clinical investigation over a long period.

SUMMARY

1. Ocular midpositioning is obtained by the stimulation of the paramedian zone of the diencephalon and the brain stem. It has also been observed on stimulation of various portions of the cerebrum (frontal and occipital) and of the cerebellum (central nodule).

† References 23 and 24.

2. In certain regions of the brain stem the eye centering is associated with body movements which may be interpreted as having the pattern of an alerting action. These eye and body movements are often accompanied by changes in the electroencephalogram.

3. The ocular midpositioning forms an integral part of the supranuclear control of the ocular movements. It probably participates in the formation of a complex system mediating an integral function of the ocular movement in coordination with the movements of the neck, body, and limbs.

4. The ocular midpositioning phenomenon, or a centering of the eyes, may be interpreted as being a patterned conjugate eye movement, just as conjugate horizontal or vertical deviations have been considered.

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POLAROGRAPHIC STUDY OF CEREBRAL COLLATERAL CIRCULATION

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THE IMPORTANCE of collateral circulation in the brain has been evident since the observations of Astley Cooper on ligation of the common carotid artery in man [1] and ligation of the principal cerebral vessels in the dog.[2]

It is also common neurological experience that there is considerable variation in capacity for adjustments in the cerebral circulation from one person to another, for carotid occlusion in one person may occur without symptoms, whereas the infarction of most of a cerebral hemisphere may follow in another. The anatomical explanation for this is, in part, the variation in size of the communicating arteries of the circle of Willis. Such variation of collateral circulation prompts the neurosurgeon to compress the carotid artery preoperatively as a test of collateral circulation before ligating this vessel. Recent experience with arteriography has shown that some persons may successfully survive for years without either one or the other carotid artery functioning, rarely without both. In later years episodes of cerebral ischemia occur as the collateral circulation becomes restricted by further vascular disease or by falls in the systemic blood pressure.[3] Records (in man) of intravascular pressure at the distal end of the carotid artery, in the circle of Willis, and in the middle cerebral vessels seldom show a fall greater than 30 to 50% when the carotid artery is occluded.*

Varying degrees of recovery in the first few days following occlusion of the smaller cerebral vessels are also seen frequently. Lack of compensation in some cases raises the question as to how much adjustment may be due to smaller anastomoses on the surface of the brain, the importance of which has recently been emphasized,[6] though their presence was known to the earlier anatomists.

In order to obtain some information concerning the mechanisms underlying this compensation in collateral cerebral vessels and their site of action, we have sought a method of plotting the effectiveness of circulation in several areas of cortex at the same time. We have chosen the polarographic method of measuring local changes in tissue oxygenation (EPG), using multiple platinum electrodes, along the lines of the investigation of coronary occlusion by Sayen and co-workers.[7] By this

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This study was supported by a grant from the National Institute of Neurological Diseases and Blindness, 1952-1953.

* References 4 and 5.

means we have been able to define the area of tissue rendered hypoxic by occlusion of a vessel and to determine the nature of changes in the bordering zone and the degree of recovery, if it occurred. We have combined these measurements with local electroencephalographic and continuous blood pressure records, and in some experiments with thermoelectric changes.

The technique of electropolarography was first used in physiological studies by Davies and Brink in 1942,[8] although the method had long been used in physical chemistry. Since that time numerous workers have used the method and have found it reliable for measuring local changes in oxygen content of tissues, including the brain. The principle of electropolarography is that the oxygen tension of an unknown solution may be measured by a platinum electrode acting as a cathode and recording the current flow between this and a nonpolarizable electrode. When the current is plotted as a fraction of the voltage, a plateau is found around 0.6 volt which is dependent upon the reaction $2H^+ + O_2 + 2$ electrons $\rightarrow H_2O_2$. Provided the voltage is maintained constant around 0.6 volt, then the current flow is proportional to the oxygen content of the solution. Since the brain is not a solution and the diffusion coefficient for brain is unknown, we have refrained from using the term oxygen content and use the term oxygen availability, as suggested by Montgomery and Horwitz.[9] Experience with the method, however, indicates to us that the local changes of tissue oxygen in brain may be extremely rapid and comparable to rates of change found in saline solutions. The assumption that the measurement at the electrode directly reflects oxygen availability in the tissue immediately surrounding the electrode appears to us to be fully justifiable.

If a recessed platinum electrode exposing only a small glass pore to the tissue is used, accurate quantitative measurements of oxygen availability may be made. Such electrodes do not reflect rapid changes in oxygen tension of tissues. We have therefore quantitated our measurements roughly by comparing them with those obtained in the resting state with the animal breathing pure oxygen (100%) and those obtained after the animal has been deoxygenated with nitrogen inhalation (0%).

Until the present investigation we do not know of any other report in which multiple, concurrently recording electrodes have been used in studying the oxygen availability of the cerebral cortex. Bronk and associates,[10] using a recessed electrode, have demonstrated that the oxygen tension of the cerebral cortex of the lightly anesthetized cat varies between 100 and 5 or 10 mm. Hg. In regions 50 μ or more from the nearest observable vessel the tension may be as low as 5 or 10 mm. Hg. As the electrode approaches an arteriole or venule, the oxygen tension rises. The unexpectedly low values in the intervascular spaces were cited as evidence of the avid cellular consumption of the low reserve of oxygen available to the cells. Alteration in the composition of the inspired air or in the pattern of respiration was promptly reflected in the oxygen tension of extravascular regions. These authors also noted that any change in the cerebral blood flow through the cortex had an immediate effect upon the gradients of tension and upon the concentration of oxygen at any point.

Davies, McCulloch, and Roseman [11] have observed a fall in oxygen content of the cat cerebral cortex during pentylenetetrazol (Metrazol) convulsions unassociated with change in blood pressure. This observation was later confirmed by Davies and Remond,[12] who showed that with EEG electrodes placed in close proximity to the

EPG electrode the fall in cortical oxygen potentials followed the seizure discharge, as recorded in the EEG. Rapid changes indicated avid consumption of oxygen by cortical neurones in vivo. Rapid fluctuations in oxygen tension of the brain, produced by alteration of the oxygenation and circulation of the blood, were also found by Davies, McCulloch, and Roseman.[11] Respiratory anoxia secondary to breathing pure nitrogen and reduction of cerebral blood flow secondary to generalized vasodilatation produced a fall in cortical oxygen levels. Conversely, a rise in systemic blood pressure following injection of epinephrine (Adrenalin) produced a rise in cortical oxygen levels.

The measured fall of EPG oxygen at the electrode in the tissue following occlusion of the local blood supply by direct pressure showed that neuronal oxygen utilization was twice as rapid after a strong electrical stimulus as in the resting state.[13] This experiment is open to both technical and physiological criticism, however, since anastomotic factors are not considered, movement artifact may have been present, and an electrical current is not an adequate stimulus. By similar compression technique it has been shown that the anemia associated with temporary carotid occlusion for 15 seconds produced no effect on the rate of cortical oxygen consumption; after 30 seconds there was an immediate but reversible depression of oxygen consumption. Severe anemias produced irreversible depression.[14] Our results confirm these conclusions.

A significant advance in the polarographic technique was the simultaneous use of multiple electrodes[9] and their use in the spatial and temporal comparison of the local change in myocardial oxygen availability following occlusion of the coronary artery.[7]

It is apparent that the oxygen measurements recorded by the polarographic electrode will depend on three major factors: (*a*) the concentration of oxygen in the general circulation, (*b*) the local blood flow, and (*c*) local metabolic consumption of oxygen. The concentration of oxygen in the general circulation can readily be maintained constant, and if the local metabolic consumption also remains constant, the electrode will then measure local blood flow. Furthermore, if multiple electrode measurements are made simultaneously with blood pressure recordings, EEG, and thermoelectric records, the local blood supply and metabolism of multiple areas of brain may be studied at the same time. Neuronal activity may be partially arrested by the administration of a sublethal dose of cyanide, thus modifying local metabolic consumption of oxygen. The behavior of the platinum electrode in all our experiments has consistently supported the validity of these assumptions.

METHODS

Observations have been made on 28 cats and 24 monkeys (Macacus rhesus). The monkey was found more satisfactory than the cat for several reasons. The cerebral circulation is comparable to that of man except that the anterior cerebral artery is a single vessel. The carotid contribution, although variable, as in man, is usually the major contributing circulation, as compared with the vertebral system.[16] An unexpected advantage has been that in two monkeys anomalies of the circle of Willis were present (absence of one posterior communicating artery), giving additional evidence in assessing the anastomotic circulation.

In many experiments respiratory exchange was controlled by a mechanical respirator connected to the tracheal cannula, and the femoral arterial blood pressure was recorded by a

Hamilton manometer. Cortical electroencephalograms (EEG) were made in all experiments with bipolar silver-silver chloride electrodes, amplified by push-pull and recorded with a three-channel Grass ink-writing oscillograph.

The polarographic recordings of oxygen availability were made with an apparatus modified after that described by Montgomery and Horwitz.[9] Continuous electrolysis is made with eight open-tip platinum electrodes in the circuit at all times. The exposed tip of these microelectrodes is small, measuring 1 mm. long and 0.1 mm. in diameter, tapering to a point. Such electrodes may be implanted in the cortex with minimal tissue damage. The electrodes are insulated to the tip with Tygon insulating paint. Leads from the electrodes to the microswitches are shielded. We have used two types of recording device. The most satisfactory method, in our experience, is to record on two or more galvanometers simultaneously by projecting the images from the galvanometer mirror on to a bromide paper camera. Six-second intervals are recorded with an Eberbach time marker. Blood pressure is recorded concurrently on the same paper. The deflections of the galvanometers may be adjusted and calibrated by altering the shunt of each instrument.

We have recorded extremely rapid changes by amplifying the direct current potentials with a cathode follower and, by use of a Brown converter acting as a chopper, have used push-pull amplification and recorded the output on a cathode-ray oscilloscope or a Grass ink-writing oscilloscope with the EEG. This method requires elaborate shielding and is subject to distortion.

The calomel cell type of indifferent electrode was discarded owing to its high resistance, and in its place we have used a silver wire electrolytically coated with silver chloride as the nonpolarizable electrode. This wire is liable to deterioration after four to six hours of use but is then easily replaced by a freshly coated wire.

In all experiments we have used pentobarbital (Nembutal) in doses of 0.5 to 0.7 gm. per kilogram of body weight as an anesthetic agent. The cerebral cortex to be examined was exposed by a wide craniotomy, and along the bony edge a plaster of Paris dam was raised, reinforced with screws in the skull. The cortex was covered in a bath of warm liquid petrolatum U. S. P., which remained at a constant temperature of about 34 C. The liquid petrolatum seals the cortex from gaseous interchange with environmental air. Very light Tygon-insulated electrodes were more satisfactory than glass-insulated electrodes, for their lightness and pliability allowed them to ride the respiratory movement of the cortex. Rigid electrodes amplify changes secondary to movement of the brain with the respiratory cycle which are minimized or absent with pliable electrodes.

The EEG and EPG electrodes were dispersed over the cortex in a manner designed to sample changes in the vascular territory examined, in the distribution of neighboring vessels, and in the area of "watershed" between them. At the beginning of the experiments the animal was deoxygenated with nitrogen for 45 seconds to obtain a near-zero oxygen level for each electrode and to enable quantitative comparison of different electrodes and procedures. Vessels were occluded by the direct application of arterial clamps or silver clips or by traction on a loose ligature previously placed about the vessels.

At the completion of each experiment the carotid artery was injected with India ink to verify anatomically the distribution of the occluded vessel. In addition, the circle of Willis was dissected and photographed and measurements made of the main branches with a micrometer microscope.

In experiments in which the effect of cervical sympathectomy and vagotomy were studied upon the course of vascular occlusion, the procedure was carried out with the electrodes in place after control occlusion readings had been made prior to neurectomy. In experiments in which the effects of stellate ganglionectomy and section of the seventh nerve were carried out, the procedure was done unilaterally prior to the occlusion and the opposite hemisphere used as a control. In one monkey the procedure was carried out bilaterally three weeks prior to study to obtain complete sympathetic denervation.

RESULTS

General Observations.—With our modification of the apparatus we have confirmed many of the findings of others. It was found that the apparatus as used by us was extremely sensitive to oxygen available to the electrode tip, both in vivo and

in vitro. When the electrodes are placed in oxygen-free saline, the current flow falls to zero. In the experimental animal, breathing pure nitrogen produces a fall to a value approaching zero of the galvanometer after 45 to 60 seconds (Fig. 1*D*). We have also found the oxygen availability of the cortical intervascular spaces to be low. High readings were obtained with the electrodes placed on or near arteries or veins. The penetration of the electrode through the cortex into subcortical white matter to a depth of 1 mm. or more reduced the galvanometer reading by 50 to 60%.

Changes in the inspired air produce characteristic responses. Pure oxygen breathing following air respiration produced a rise of cortical oxygen availability of 30 to 50%. Nitrogen inspiration caused a rapid fall beginning within 4 seconds, and the low level reached after 45 seconds was used as an arbitrary zero. The addi-

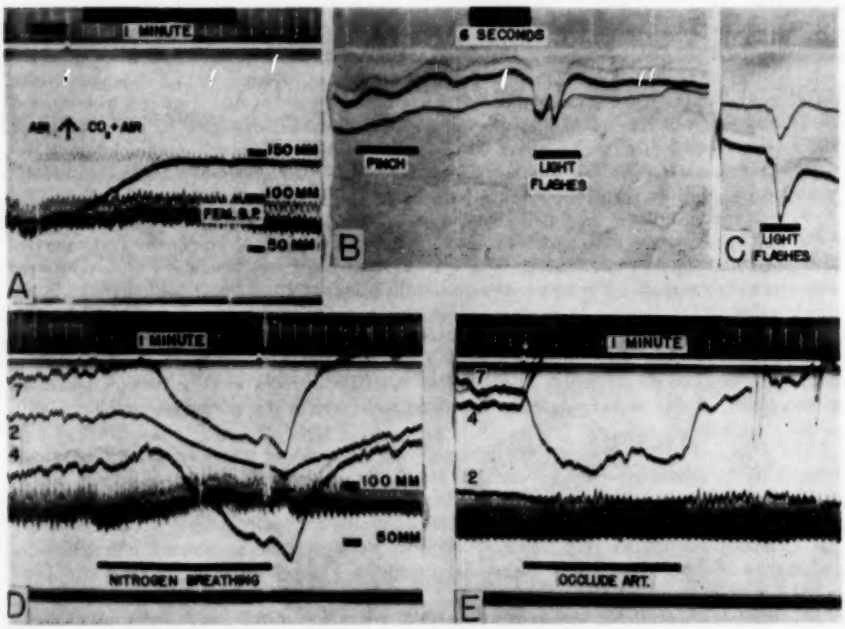

Fig. 1.—*A*, combined femoral blood pressure and polarographic cortical oxygen recording from the parietal region showing the effect of breathing 5% CO_2 and air mixture after respiration of air alone.

B and *C*, faster recording of the effect of painful stimulation and 2-per-second retinal light flashes upon cortical polarographic potentials, recorded from left occipital (double trace) and occipitoparietal (single trace) regions, with the animal under light anesthesia.

D, effect of nitrogen breathing on femoral blood pressure and on temporal and occipital oxygen tension. The three polarographic tracings are from Points *7*, *4*, and *2*, shown on the diagram in Figure 2.

E, occlusion of small Sylvian branch of the left middle cerebral artery. Electrode *7*, shown in the diagram in Figure *2*, is in the mesial parietal distribution of the vessel; Electrode *4* is in the occipital anastomotic zone, and Electrode *2* is in the left temporal area, proximal to the point of occlusion.

tion of 5 or 10% CO_2 to the inspired gas produced a rise in cortical oxygen availability after respiration of air (Fig. 1*A*) but seldom caused a rise after pure oxygen breathing because of coincident fall in blood pressure. Asphyxia by obstruction of

the respiratory passages caused rapid respiratory effort, a fall in blood pressure, a rise in the temperature of the cortex, and a fluctuant fall in the oxygen availability of the cortex.

Greatly increased metabolism of oxygen during neuronal activity has been demonstrated by the slight, but significant, fall in oxygen availability in the occipital cortex associated with a light rapidly flashed on the retina (Fig. 1*B* and *C*). The demonstration of such effects requires an extremely light degree of anesthesia. In deeper anesthesia arousal by cutaneous stimulation was associated with momentary fall of potential in all areas, followed by a large slow rise. A temporary rise of cortical oxygen availability above the resting state also occurs with the resumption of oxygen breathing following nitrogen breathing, or the administration of cyanide with abolition of the EEG, provided there is no significant fall in systemic blood pressure (Fig. 1*D*). This rise is probably due to decreased neuronal oxygen consumption. We have sometimes seen a slight rise in cortical polarographic readings following supplementary doses of barbiturate, but since the latter experiments have been carried out on animals already anesthetized, the results were frequently complicated by a fall in systemic blood pressure.

Continuous EEG and blood pressure records and cortical oxygen polarography readings in the monkey for as long as two hours following injection of 40 units of regular insulin did not show changes comparable to those of cyanide. Slight, independent, periodic rise of oxygen tension occurred, and the EEG showed some periodic slow activity.

We have not seen a significant change in resting cerebral oxygen availability following stimulation or section of the cervical sympathetics in cat or monkey, or following stellate ganglionectomy or section of the facial nerve. We have, however, seen a significant fall in oxygen availability in the temporalis muscle and occasionally an associated rise in cortical oxygen availability following sympathetic stimulation in the monkey, suggesting a shunt from extracranial to intracranial circulation.

The EEG is a more sensitive indicator of the depth of barbiturate anesthesia than the cortical oxygen polarogram. In the EEG slow waves are followed by barbiturate bursts and later by fast activity as the depth of anesthesia decreases with continuous recording for eight hours, but the oxygen polarographic readings remain remarkably constant or show slight decrease.

The rapid cerebral hypoxemia caused by nitrogen inhalation was reflected in the oxygen polarographic record before any change was evident in the EEG. Inhalation of nitrogen caused a fall in polarograph readings beginning within four seconds if the gas was supplied directly to the tracheal cannula. When the fall in the polarograph record was longer delayed, owing to large respiratory dead space or slow respiration, as in Figure 1*D*, the changes of the EEG were correspondingly delayed. The EEG disappeared some six to eight seconds after the polarograph reading had reached its maximum fall. The sequence of events on nitrogen breathing was as follows: A fall of cortical polarograph readings by 30 to 50% occurred; the EEG then began to show decreasing amplitude and slowing of fast activity. Further reduction, of 50 to 60%, of oxygen potentials was accompanied by flattening of the EEG record except for bursts of slow waves similar to the so-called pentobarbital bursts. The slow-wave activity disappeared some six seconds after the polarograph readings reached zero. Readministration of oxygen recapitulated the sequence of changes in reverse. The EEG slow waves reappeared; then the polarograph readings

rose, and the interburst fast activity reappeared when the cortical oxygen potentials had reached 65 to 75% the initial reading. The EEG fast activity bore a closer relation to the cortical oxygen availability than did the slow-wave pattern.

EEG changes associated with vascular occlusion bore relation to polarograph readings only if bipolar EEG electrodes were placed in proximity to the EPG electrodes. Occlusion of a vessel could cause some degree of fall in oxygen potentials unassociated with EEG changes if the reduction of oxygen availability was less than 20%. A reduction greater than 20% led to lessened amplitude of the EEG with slowing. This change in the EEG usually occurred six to eight seconds after the EPG began to fall. When a zone of cortex was rendered totally anoxic, the EEG

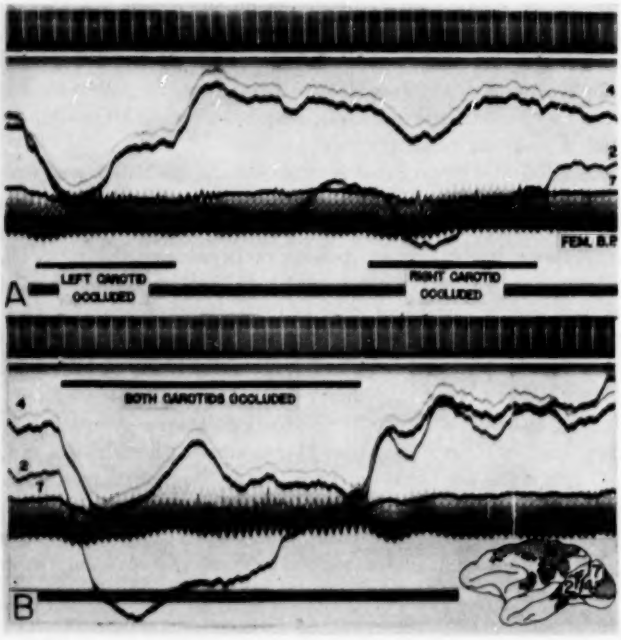

Fig. 2.—*A*, effect of temporary unilateral common carotid artery occlusion on cortical oxygen tension. Electrodes and blood pressure as in Figure 1*D*.

B, effect of temporary bilateral occlusion of the common carotid artery. In all procedures, femoral blood pressure was recorded concurrently. Electrode positions shown in insert; stippled area represents regions filling with India ink from injection of vertebral arteries after ligation of carotid arteries.

disappeared when the oxygen availability had been reduced by 80%. When the vessel was released, slow, low-amplitude activity in the EEG reappeared after a 20% increase in oxygen availability and was restored to normal when the polarograph reading rose to 80% of the resting figure. During the supernormal phase the EEG showed no further change.

Carotid Artery Occlusion.—Occlusion of a cerebral vessel was accompanied by a fall in cortical oxygen availability, the extent and duration of which depended upon the size of the vessel occluded and the degree of functioning anastomotic circulation.

With release of the occlusion there was prompt return of the cortical oxygen potentials to initial readings or higher (Figs. 1*E*, 2*A* and *B*, and 3). When the carotid artery is occluded, care must be taken not to stimulate a vagal depressor reflex, for the associated fall in systemic blood pressure then augments the polarographic fall due to the vascular occlusion and its subsequent recovery.

Occlusion of one common carotid artery caused a slight transient generalized cortical hypoxia, which was maximal in most instances over the ipsilateral Sylvian area. Since the anterior cerebral artery in the monkey is a single vessel to which both anterior cerebral arteries contribute, there is commonly a fall in polarographic readings in both hemispheres when one carotid is occluded (Figs. 2*A* and 6). The fall in the contralateral hemisphere is chiefly in the territory of supply of the middle cerebral artery. The area of supply of the anterior cerebral artery on both sides may show a delayed paradoxical rise, owing to the enlargement of circulation through the point of junction of the two anterior cerebral arteries (Fig. 6). This shunt effect was more commonly seen in the cat than in the monkey.

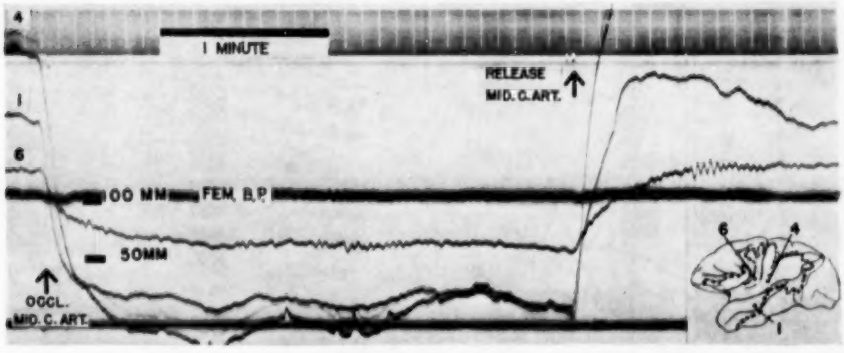

Fig. 3.—Mean femoral blood pressure and simultaneous cortical oxygen recordings after occlusion of the left middle cerebral artery. Incomplete "escape" is seen in Electrodes *1* and *4*. The position of the electrodes is shown in the insert, where the broken line encloses the area that failed to fill with India ink injection when the middle cerebral artery was occluded after the animal was killed.

When both carotid arteries were occluded, the remaining circulation depended not only upon the posterior communicating arteries, but also on the effectiveness of communications between the posterior cerebral arteries and the branches of the middle and anterior cerebral arteries on the surface of the occipital lobe. The initial fall in this "watershed" occipital control area following bilateral carotid occlusion was followed by a compensatory rise in readings, which begins to develop after 15 to 20 seconds of continued occlusion. This compensation was commonly rhythmical and developed independently and irregularly in different areas of the watershed (Fig. 2*B*). The compensatory process was finally reflected in a slighter and later rise in the areas more exclusively supplied by the occluded vessel. Immediately following release of the carotid occlusion there was recovery of the readings in the ischemic area. In border zones that had previously shown compensatory rise during the period of occlusion, the recovery on release commonly exceeded the previous resting level. This supernormal recovery phase, or "rebound," therefore indicated that the

preceding process of compensation had involved an increase of vascularity which now persisted in these zones for one-half to two minutes. Occlusion of both carotids and both vertebrals resulted in a generalized fall in all cortical readings to nitrogen zero in spite of an associated rise in blood pressure. An extensive supernormal phase in the whole cortex followed release of all the main vessels and was associated with a continued rise in blood pressure for many seconds.

The events of compensation and rebound supernormal phase were also seen after occlusion of the ipsilateral carotid artery (Fig. 2*A*). The delay in recovery in Electrode 2 in this Figure indicates the degree of variability of the recovery process, which at times could be extremely delayed in one small area or another, possibly owing to local metabolic factors. The process of compensatory rise during occlusion

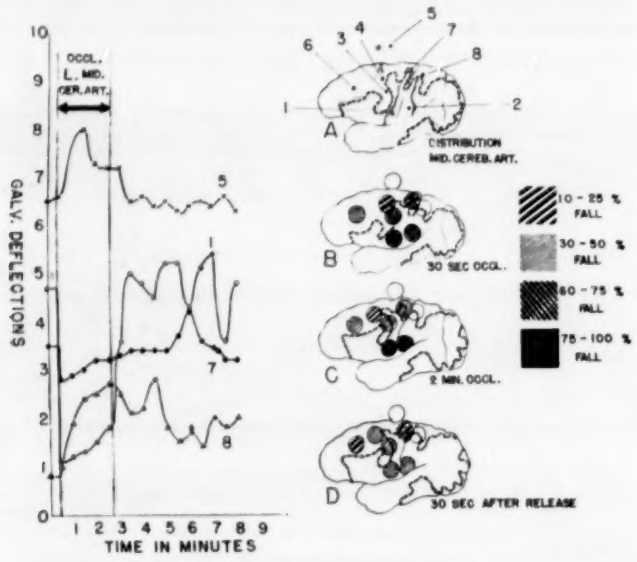
OCCL. L. MID. CER. ART.
GALV. DEFLECTIONS
TIME IN MINUTES
DISTRIBUTION MID. CEREB. ART.
30 SEC OCCL.
2 MIN. OCCL.
30 SEC AFTER RELEASE
10 - 25 % FALL
30 - 50 % FALL
50 - 75 % FALL
75 - 100 % FALL

Fig. 4.—Combined topographic brain charts of oxygen changes and plots of the galvanometer changes in four of the eight electrodes in a Macacus rhesus monkey, showing effect of occlusion of left middle cerebral artery for two minutes. The changes in all the eight electrodes are shown in the diagrams on the right of the Figure. The spectrum of falls in oxygen tension in the ischemic zones with "escape" and rises in the anastomotic zones (in the territory of supply of the anterior cerebral artery and in the opposite hemisphere) is represented by shading of electrode sites.

and rebound on release of occlusion was associated with localized increase in cortical temperature, which was recorded by a thermocouple in a few experiments. Observations for as long as 30 minutes following occlusion show that a steady state is reached after 4 to 5 minutes. Compensation was present whether the animal was breathing oxygen or 10% CO_2 and oxygen, and it was unaffected by sympathectomy, stellate ganglionectomy, or section of the ipsilateral seventh nerve. If EEG was severely affected or abolished during the period of occlusion, compensatory recovery in the polarograph reading was associated with reappearance of the EEG in the neighboring EEG electrode. Rebound after recovery was not associated with any

change in the EEG. The reverse experiments of occlusion of both vertebral arteries, the carotids remaining patent, created a border "watershed" zone along the edge of the occipital lobe, with marked compensatory increases in this zone.

If one carotid artery was already occluded, occlusion of the second carotid artery led to a very rapid and severe ischemia of the second hemisphere, becoming maximal after eight seconds (Fig. 6), more rapidly than with occlusion of the second carotid artery alone. This degree of ischemia is due probably to the sudden reduction of blood volume in a large vascular bed associated with the compensatory dilatation in the ipsilateral hemisphere.

The degree of initial fall following occlusion of any of these vessels was related to the presence and size of the collateral circulation, as judged by the size of the posterior communicating arteries after the killing of the animal. For example,

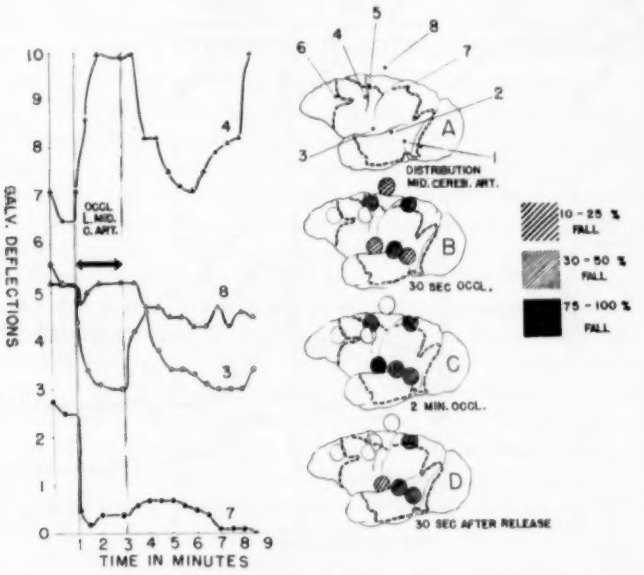

Fig. 5.—Records similar to those in Figure 4, from a different experiment. Occlusion of the left middle cerebral artery for two minutes is accompanied by a rise in the anastomotic zone (anterior cerebral artery), fall without escape in the left Sylvian area, and incomplete compensatory escape with failure of recovery in the left parietal region. Instability is seen for several minutes after release.

measurements of the size of the posterior communicating arteries showed that the fall in potential in the center of the territory of the middle cerebral artery was moderate or large according to whether this vessel was large or small. In one case a fall to zero over the whole middle cerebral zone with poor recovery during carotid occlusion was found to be related to absence of the posterior communicating artery on that side. The degree of compensation during occlusion was not directly related to the degree of initial fall (Fig. 2*A* and *B*).

We therefore concluded that the initial ischemia resulting from occlusion of one or both carotid arteries in the monkey was directly related to the size of the posterior communicating arteries. A compensatory process beginning within 15 seconds and

developing irregularly and independently in areas bordering the ischemic zone reached a maximum effectiveness in 1 to 3 minutes. This recovery was associated with increased vascularity in the bordering areas, which persisted for one-half to one minute after release of the occluded vessel. It was not related to sympathetic or parasympathetic nerve supply and was probably determined by tissue metabolites.

Middle Cerebral Artery Occlusion.—Occlusion of the middle cerebral artery resulted in ischemia which was in general related to the center of an area that, after injection with India ink, proved to be the territory of supply of that artery (Figs. 4 and 5). In this case, however, the process of compensation and recovery occupied unexpectedly large areas. Only the gyri bordering the Sylvian fissure showed a fall of 75 to 100% of the galvanometer deflection (Figs. 4 and 5). It is evident that in

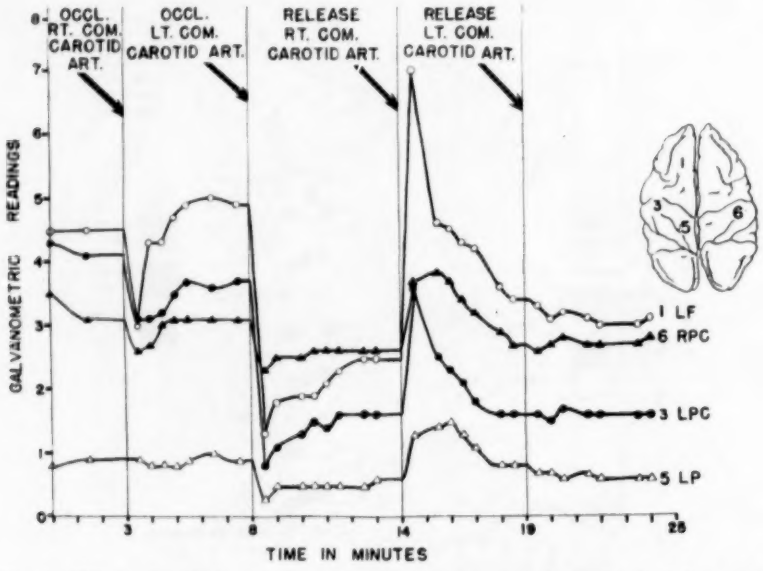

Fig. 6.—Effect of occlusion of the left carotid artery, the right already being occluded. Escape is seen in left frontal region after occlusion of right common carotid artery. A more rapid and severer degree of fall in all polarograph electrodes is seen after the second carotid artery is occluded, though some compensation still occurs.

LF indicates left frontal; *RPC*, right postcentral; *LPC*, left postcentral, and *LP*, left parietal.

this case considerable local readjustments of circulation take place over a very wide area. In spite of this, specific points bordering the Sylvian fissure showed a slowly progressive type of failure (e. g., Point 3, Fig. 5). Points bordering the territory of the anterior cerebral artery could show either a partial fall (Point 6, Fig. 4) or a rapid rise or "shunt" effect (Point 4, Fig. 5). Such rises were found to be associated with slight rise in temperature, as shown by the thermocouple.

It was surprisingly difficult to render a large zone of cortex totally ischemic by the occlusion of a single vessel. Occlusion of a small artery rendered a small area partially ischemic with great increase in vascularity of neighboring areas (Fig. 1*E*). At the end of a long experiment, when blood pressure was falling, the clipping of

large supracallosal branches of the anterior cerebral artery, or of the main trunk of the middle cerebral artery, produced large areas of ischemia, with only minimal compensatory response. Further evidence that the level of systolic blood pressure is a critical factor in the compensatory process will be discussed below. That a fall in polarograph reading in the ischemic area is due to inability of blood supply to replace tissue consumption of oxygen was confirmed by the use of potassium cyanide to inhibit oxidation. After an intraperitoneal dose of cyanide the first effect noticed was a reddening of the venules of the brain and a rise, sometimes very large, in all polarograph potentials. At this time, before cardiac failure had become obvious, occlusion of the carotids, or of any cerebral vessel, produced only a very slow and slight fall in cortical potentials. If cyanide was administered after a vessel had been occluded, the cortical potentials near the border "watershed" areas rose, but not those in the area of compensation or those in which a fall had persisted after the occlusion. These findings provided additional evidence that the oxygen consumption by the tissue accounts for the fall in galvanometer readings in anoxic areas, and increased blood supply for compensatory recovery, when that occurs.

Evaluation of Therapeutic Measures.—Neither the pattern nor the speed of recovery process was affected by cervical sympathectomy (12 experiments), stellate ganglionectomy (3 experiments), or section of the seventh nerve, which the work of Chorobski and Penfield [15] showed to contain cerebral vasodilator fibers. Change of respired gas to 5% CO_2 and oxygen when pure oxygen had previously been administered produced no observable effect on the recovery curve (five experiments). Recovery was more ample in all phases when oxygen was substituted for air, but in this case it was the maximum potentials that were altered (including the resting potential before vascular occlusion), and not the lowest potential reached or the duration of minimum potential. The administration of CO_2 and oxygen mixture following breathing of pure oxygen sometimes resulted in a fall of oxygen potentials. This effect was related to a concomitant fall of blood pressure. Indeed, in none of our experiments was there any remarkable vasodilator effect dissociated from change in blood pressure caused by administration of carbon dioxide and oxygen mixture following oxygen breathing. A slight vasodilator effect was occasionally noted when a CO_2 and air mixture followed air breathing (Fig. 1). Schmidt and associates [16] have commented on the slight or doubtful effect of carbon dioxide on the cerebral vessels of the monkey.

Importance of the Level of Systolic Blood Pressure.—The simplest method of changing systolic blood pressure is to raise or lower the trunk and lower limbs of the animal, with the head and upper limbs in fixed position. The blood pressure was recorded from the brachial artery. When the trunk and lower limbs were raised, the brachial systolic blood pressure rose to 130 mm. Hg; when they were lowered, the systolic blood pressure fell to 20 mm. Hg. With changes in blood pressure of this degree the oxygen availability of the cerebral cortex followed the falls passively. Smaller falls of blood pressure, however, showed slight compensation of the EPG independent of the blood pressure.

When a vessel was occluded in the presence of a very low blood pressure, the compensatory mechanism of the collateral circulation ("escape") was abolished. If the blood pressure was now gradually increased, a critical level was reached at 60 mm. Hg, when the polarograph reading in the area of ischemia suddenly rose.

Similarly, if a cerebral vessel was occluded in the presence of an elevated blood pressure, the bordering anastomotic zone showed the usual phenomenon of escape and supernormal phase, but both were abolished when the blood pressure was reduced to low levels. While the polarograph readings followed the blood pressure passively in the bordering zone, the electrodes with very low readings in the central ischemic zone showed minimal and delayed changes, with gross alterations of blood pressure. This observation is additional evidence that the bordering rise in oxygen availability around an ischemic zone is due to an increased blood flow. Several minutes after the intraperitoneal injection of sodium cyanide the potential of the border zone was reduced by 75%, and the degree of response to postural change in the border zone was as poor as that of the central ischemic area, convincing us that the vasodilatation in the bordering area is mediated in some way by the effects of neuronal metabolism. Vasodilators, such as amyl nitrite, also impaired the mechanism of compensation by causing a fall in systemic blood pressure.

In these experiments, the most important single factor in maintaining the anastomotic circulation and limiting the degree of local hypoxia was maintenance of the blood pressure at optimum levels. Shock was devastating to the compensatory escape mechanism. In the presence of shock the anastomotic circulation to an ischemic zone failed. A significant fall in blood pressure impaired the compensation mechanism, elevation of the blood pressure in this situation by posture, warmth, epinephrine, and oxygen restored the mechanism.

COMMENT

Oxygen polarography appears to be a reliable method for continuous recording of oxygen availability in the cerebral tissue spaces in vivo. The oxygen available to the electrode tip depends on the rate of oxygen diffusion from the blood vessels and the rate of its utilization by neuronal metabolism. The gradient of oxygen measured may be affected by interruption of blood flow or by inhibition of neuronal respiration by the use of cyanide. Thus, after prolonged ischemia the oxygen electrode records local oxygen changes due not only to diminished blood supply but also to the diminished utilization of oxygen by the damaged tissue.

From our observations it is evident that in spite of the extreme vascularity of the cerebral cortex there is but a narrow margin of oxygen reserve. This reserve will support cortical neuronal function for some 10 seconds, as shown by correlation of the EEG with the EPG following nitrogen and vascular occlusion. It is also evident that neuronal consumption of oxygen in the cortex is high, even under the influence of barbiturate anesthesia, for there is a steep gradient of oxygen tension between arteriole and tissue, and there is a rapid fall of oxygen potentials associated with occlusion of a cerebral vessel. Cyanide, by impairing neuronal utilization of oxygen, rapidly depressed EEG activity and elevated the cerebral oxygen potentials. Insulin did not cause the same order of change within two hours after injection, presumably because glucose and glycogen stores had not been exhausted within this period of time.[17]

When the monkey is under barbiturate anesthesia and is breathing air, there is a surplus of oxygen in the tissue such that a reduction of 10 to 40% of the polarograph reading is necessary before any change in EEG can be detected in any given area. When the animal is breathing oxygen, this surplus level of tissue oxygen availability is greater (30 to 50% of the reading with nitrogen value as zero). The

level of availability at any moment is directly dependent on the level of systolic blood pressure. Though there is some degree of compensation following any given rise or fall, tending to lessen the effect of the blood pressure change, this type of compensation is very little more than the corresponding compensation in the blood pressure itself. The remarkable compensation in cerebral flood flow in unanesthestized man following change from head-down to head-up position, found by Shenkin and associates,[18] is therefore not reflected in our oxygen readings. This may be due to the presence of anesthesia in our experiments, and we do not have data on the rate of blood flow. It is clear, however, that when the blood pressure fell below 50 mm. Hg, the cortical oxygen potentials fell below the critical level and EEG changes ensued.

Apart from its striking dependence on the level of systolic blood pressure, the tissue oxygen availability in the cerebral cortex shows remarkable compensation to the effect of occlusion of a blood vessel. When a small blood vessel is occluded, there is an immediate rise in the whole bordering area supplied by other vessels. When a larger vessel is occluded, such as the middle cerebral artery, there is a delay of 10 to 30 seconds before bordering areas reflect a similar rise in oxygen potentials, which, nevertheless, may assume large proportions and outlast the period of occlusion. This reaction was found to be related to vasodilation of the smaller collateral vessels, was independent of the presence or absence of sympathetic or parasympathetic innervation, but was abolished by inhibition of tissue oxidation by cyanide. It is therefore presumed to be the result of local vasodilation of collateral small vessels by tissue metabolites originating in the ischemic area. It proceeds independently in different areas, sometimes with rhythmical fluctuation. This compensatory process is also sensitive to the level of systolic blood pressure and was found to be absent when the blood pressure was below 60 mm. Hg. It was greatly improved by a rise of blood pressure (e. g., from 60 to 120 mm. Hg).

This compensatory process was also evident in relation to the ischemia following occlusion of one or both carotid arteries. In this case, however, three complicating factors must be taken into account. First, the degree of initial fall in potentials relates to the site of the posterior communicating artery and that of the common anterior cerebral artery. Second, the occlusion of such a large vessel commonly results in a slight rise in systemic blood pressure, immediately reflected in a rise in potentials in the opposite hemisphere and in the ipsilateral occipital pole. Lastly, the initially ischemic bordering areas of the same hemisphere show a delayed rise in oxygen potentials of the kind found to surround smaller ischemic areas. In some instances the extent of this bordering hyperemia was remarkable, being separated from ischemic areas by more than 1 cm. with independent regional fluctuations. Yet we were not able to demonstrate any mechanism other than local tissue response for such a widespread effect. Though under some circumstances, localized injury to the cortex can result in slowly spreading effects (the spreading depression of Leao), the studies of Marshall and associates [19] have indicated that such effects spreading to a distance do not occur when the cortex is bathed in liquid petroleum at body temperature, as in all our experiments. We therefore have no direct information as to the mechanism of such spread of a locally vasodilating mechanism to neighboring areas. Saturation of the tissues with 10% carbon dioxide prior to occlusion of the vessel did not inhibit this widespread compensatory effect, and it is therefore unlikely that carbon dioxide is of any importance in this reaction.

Ischemia of cortical nerve tissue results in damage to the tissue. The method used by us did not give direct evidence of the extent of such damage, though it was apparent that the region of an electrode which had exhibited a basal or near-zero oxygen potential for more than 30 seconds exhibited a steep recovery of potential to supernormal level on release of the vessel from compression, as in Electrode 4, in Figure 3. Here oxygen supply greatly exceeded a reduced or absent tissue demand. With shorter ischemia or a slighter degree of ischemia, the rise in potentials was less steep, indicating that tissue consumption had exceeded supply. Without further data it was not possible to separate completely the supernormal potential after release due to lack of tissue demand from that due to vasodilation. It is likely that all vessels in the ischemic area are maximally dilated after the first 60 seconds.

In three experiments, a situation seen in man with chronic occlusion of one carotid artery was simulated. Digital compression of the patent carotid vessel in man suffering from carotid occlusion has been shown by us to produce paroxysmal slow waves in the EEG recorded from the intact hemisphere, frequently associated with clonic movements in the limbs opposite the digitally compressed vessel. We have also seen spontaneous seizures involving the limbs on the same side as the occluded carotid artery in man, due to transient falls in blood pressure in the presence of chronic carotid occlusion. In both the cat and the monkey, occlusion of the second carotid artery, the other having previously been occluded, caused a precipitous fall in oxygen readings over the ipsilateral hemisphere, being maximal in eight seconds and more precipitous and severer than over either hemisphere when one carotid artery alone or the two simultaneously are occluded. The fall in oxygen availability is associated with the appearance of slow waves in the EEG. It is possible that this means that the gradient of cortical hypoxia is of importance in the genesis of epileptic seizures, and the area of ischemia being larger in the ipsilateral hemisphere when the other carotid artery is occluded accounts for the pattern of convulsions seen in man with chronic occlusion of one carotid artery.

We have found no evidence to suggest that gentle occlusion of a cerebral artery is accompanied by vascular spasm. We have attempted to avoid marked traction or stretching of vessels, which we have no doubt may cause spasm of a vessel. The development of collateral circulation is best aided by oxygen breathing and by maintenance of blood pressure at optimum levels. Stellate ganglionectomy, cervical sympathectomy, section of the seventh nerve, and vasodilating drugs do not seem to be of any therapeutic benefit and, if they cause a fall in blood pressure, may be harmful.

CONCLUSIONS

Multiple, simultaneous records of the oxygen availability of the cerebral cortex in monkeys and cats have been made by the polarographic method simultaneously with cortical thermoelectric records, the blood pressure record, and the EEG. Such records gave consistent, reliable data concerning local blood flow and the metabolism of the brain. The following observations were made:

1. After occlusion of one or both carotid or vertebral arteries the severity and duration of the ischemia of the cortex depends on the contribution of the anastomotic vessels.

2. Occlusion of the middle cerebral artery or of a small cerebral vessel is followed by a fall in the local oxygen availability in the distribution of the occluded

vessel, which is maximum after 8 to 12 seconds. There is a bordering zone in which the tissue oxygen availability is unstable and an outer, anastomotic zone in which the tissue oxygen availability and temperature rise, owing to increase of the local collateral circulation.

3. The area of ischemia is minimized by breathing pure oxygen and is increased by a fall in blood pressure. The collateral circulation is not improved by cervical sympathectomy, stellate ganglionectomy, or section of the seventh nerve roots, unless there is a coincident rise in blood pressure.

The local bordering hyperemia following vascular occlusion appears to be dependent on local metabolic factors. In the monkey, it seems likely that CO_2 is a relatively unimportant metabolite in this respect. Continuing metabolism throughout the areas bordering the ischemic zone was revealed by increased polarographic readings in these areas, as well as in normal cortex, following the administration of cyanide. The temperature of local zones of collateral circulation rises and the process shows independent, often rhythmical, fluctuations.

Electroencephalographic changes have been correlated with changes of cerebral oxygen availability. After the production of cerebral ischemia or anoxia, the local tissue oxygen falls steadily until minimal values are reached, after 8 to 12 seconds. The corresponding disorganization of the EEG follows, with a time lag of five or more seconds.

The maintenance of the systemic blood pressure at optimum levels and the administration of oxygen are the most potent aids to development of collateral circulation in the treatment of cerebral vascular occlusion. Sympathectomy does not appear to be of significant therapeutic value.

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PSYCHIATRIC AND NEUROLOGICAL SIDE-EFFECTS OF ISONIAZID AND IPRONIAZID

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THE ADVENT of a new drug which is capable of causing convulsions, psychoses, and peripheral neuropathy as side-reactions is of interest to psychiatrists. If this drug is being widely used, it is important for us to be aware of its dangers. Such a drug is isoniazid (isonicotinic acid hydrazide; Rimifon), with its isopropyl derivative iproniazid (Marsilid). Although isoniazid was first synthesized in 1912, its use was not discovered until 1951. Early in 1952 it was suddenly announced in the newspapers as a miracle drug for the cure of tuberculosis. Although it has not lived up to the original fantastic claims, it is now being used for about one-half of the patients who are under treatment for tuberculosis in this country because of its effectiveness, ease of administration, and cheapness. Undoubtedly hundreds of thousands of patients all over the world are being treated with it.

It was soon found that by weight isoniazid was about 600 times as effective as *p*-aminosalicylic acid (PAS) and 50 times as effective as streptomycin against the tubercle bacillus,[1] and that clinically it was far more successful in relieving tuberculosis symptoms than even streptomycin. It seemed to operate by inhibiting the respiration of the Myobacterium tuberculosis, particularly that phase involving pyridoxine (Vitamin B_6).[2] Early in 1952, even in the first scientific papers about the new drug, many toxic symptoms were listed. Robitzek and Selikoff, at Sea View Hospital,[3] described these symptoms as follows:

1. Those referable to autonomic stimulation: dryness of the mouth, constipation, delayed micturition, difficulties in visual accommodation.

2. Those referable to central nervous system stimulation: vertigo, muscle twitching, hyperreflexia, excitement, euphoria, somnolence, convulsions, and psychoses.[4]

3. Those due to Vitamin B antagonism[5]: peripheral neuropathy, glossitis, cheilosis, pellagra,[6] and a Korsakoff-like psychosis.[7]

These toxic effects were described as severer in unstable personalities and patients with a previous history of psychosis or convulsions[8] and as more frequent in older patients[3] and in alcoholics.[8] The degree of toxicity was found to be proportional to the plasma level of the isoniazid.[1] Experimental animals after a lethal dose always died in convulsions,[25] and several deaths in humans were reported, usually following convulsions.* Iproniazid, although at first believed to be less toxic, was soon found to cause many more mental symptoms than isoniazid[4] and for this reason is available for experimental use only, and in fact, has been given up completely by most physicians.[13] Of 44 patients treated with iproniazid in three tuber-

* References 9-12.

culosis sanatoriums in Connecticut, 6 developed psychoses which required mental hospitalization, and only 4 have recovered.[14] Soon reports began to appear listing such toxic symptoms as fatigue,[15] irritation of the eyes,[16] increased libido,[12] decreased libido,[17] headaches and spots before the eyes,[17] pressure on the head,[15] and a large group of subjective complaints of this caliber, which are too familiar to the psychiatrist to require further mention. Such reports, combined with statements like "This drug should not be given to epileptic patients,"[18] together with reported toxic deaths, no doubt led to the belief that isoniazid and iproniazid were very dangerous drugs. However, more temperate and careful studies soon began to appear about isoniazid. The British Medical Research Council[19] reported that toxic reactions were negligible with isoniazid in doses of 4 mg. per kilogram of body weight per day, and the United States Public Health Service[20] reported on 1,600 patients treated with 3 mg. per kilogram per day and showed that there were practically no toxic symptoms and that the smaller dosage was as effective as the previously used dose of 18 to 40 mg. per kilogram per day. Biehl and Skavlem[21] showed that when a group of patients who were without toxic symptoms on a smaller dose had the dose raised to 16 to 24 mg. per kilogram peripheral neuritis appeared in 37%. All the autonomic symptoms and many of the subjective complaints could not be confirmed. The American Trudeau Society officially reported that fatal reactions were "extremely rare" and that even with the excessive dose which many continued to use, severe reactions occurred in only 1%.[22]

Although serious psychiatric symptoms were common after iproniazid, a careful search of the literature by Bennett, Cohen, and Starer[4] disclosed only 16 reported cases of psychosis caused by isoniazid. Even the early claims of the activity of isoniazid in causing a frequently welcome elation and increased psychomotor activity[3] were denied in a recent editorial of *The Journal of the American Medical Association*[23] based on a careful study of mentally normal tuberculosis patients before and after the administration of isoniazid.[24] The epileptogenic effects of isoniazid were considered dangerous, but Reilly and co-workers[25] showed that even 40 mg. per kilogram in a single dose would not regularly cause convulsions in patients normally free of seizures, although they cautioned that a history of fits should be sought for. Dr. MacKinnon† has shown that a normal EEG is not affected by intravenous injections of large amounts of isoniazid, although it tends to aggravate abnormalities. The convulsant effects of isoniazid are attributed to the hydrazide group and are common to all unsubstituted hydrazides; they are, therefore, less evident in iproniazid.[25]

Many authors continue to appeal for higher dosage‡ on the theory that larger amounts must be more effective. In Continental Europe, therapeutic dosages of 20 to 40 mg. per kilogram per day are common while 10 mg. per kilogram for tuberculous meningitis is recommended as a daily dosage.[27] Apparently, these physicians are unaware of the fact that the toxic symptoms are proportional to the plasma level and that the therapeutic effect does not increase when the dosage is raised above 3 to 4 mg. per kilogram per day.[20] Attention has been drawn to the danger of diminished renal function, as isoniazid is excreted by the kidney.[18] A

† MacKinnon, I. H.: Personal communication to the author.

‡ References 25 and 26.

careful review of the literature and of the cases of toxicity which are described below show that practically all the psychotic reactions occurred in patients with daily doses of 8 mg. or more per kilogram per day or with iproniazid.

Because of the early reports that isoniazid produced increased psychomotor activity and euphoria, this drug was soon tried in the treatment of mild depression [28] and major psychoses§, with conflicting results, the earlier workers reporting good effects and the later, more careful workers reporting failures except in the treatment of delirious reactions to tuberculosis, where it has proved to be so effective that such cases are now rarely seen.[30] It has been shown repeatedly that the chronic toxicity differs from the acute side effects.[25]

RESULTS

These results are based on observations of 602 patients who had been treated with isoniazid at the Edgewood Division of Pilgrim State Hospital between March, 1952, and March 17, 1954. All the patients, with a few exceptions noted below, were given isoniazid, 4 mg. per kilogram per day in three divided doses by mouth, and streptomycin 1 gm. intramuscularly every third day. The duration of isoniazid therapy in these patients varied from two years to two weeks. The males and females were in the proportion of 1.5:1; there was no observable difference in the reaction according to sex. The ages varied from 14 to 93. Despite statements in the literature to the contrary, there was no observable difficulty with patients in the older age groups, even those with advanced cerebral arteriosclerosis.

In addition to the 602 patients personally observed during their isoniazid treatment at Edgewood, all patients in tuberculosis hospitals in New York City and Nassau and Suffolk Counties who developed psychoses requiring certification while under treatment during this two-year period were sent to the Pilgrim State Hospital, and their records were carefully studied for the purpose of this report. About half of all the patients in tuberculosis hospitals around New York City are now receiving isoniazid or iproniazid or both. The admission rate to Edgewood from these tuberculosis hospitals amounts to approximately 2 patients per week, a total for the two-year period of about 200 patients. As most of these admissions were continued on treatment with isoniazid, they are included in the 602 patients mentioned above. A few were considered to be suffering from a psychosis precipitated by drugs, on admission to Edgewood. They are discussed in Section I; none of the patients treated at Edgewood developed new psychotic symptoms from the isoniazid administered there, although agitated episodes occasionally occurred.

I. *Psychotic Reactions to Isoniazid.*—The records of these new admissions showed that in many cases the physicians at Bellevue or Kings County or at the tuberculosis hospitals in which they had been under treatment had mentioned the diagnosis of isoniazid psychosis. However, there has been no noticeable increase in the number of patients transferred in this way from tuberculosis hospitals to Pilgrim State Hospital since the advent of isoniazid, and most of these patients could more readily be classified in one of the customary categories. In a few cases, however, the history and appearance of the patient and the subsequent course gave unequivocal evidence of a toxic psychosis, including a fairly sudden onset after a

§ References 29-33.

period of drug therapy, with clouded sensorium, agitation, and auditory and visual hallucinations. Such cases were uncommon, but, in addition, there were a number in which one of the functional group of psychoses appeared suddenly to have developed after administration of these drugs and rather quickly cleared up as soon as the drug was discontinued. In most of those patients who were selected for this paper as having isoniazid psychosis, a period of alleviation of symptoms when the drug was stopped and recurrence when the drug was started had been observed. When the patients were selected in this way, the number who were finally considered to have isoniazid or iproniazid psychosis were as follows:

Psychosis due to another drug (isoniazid)	16
Psychosis due to another drug (iproniazid)	9

An illustrative case of each follows.

Isoniazid Psychosis: M. B., No. 46826, white woman, age 31, admitted June 2, 1952. Patient had been treated at Sea View Hospital from 1942 to 1945 and at Metropolitan Hospital from Sept. 12, 1949, to May 9, 1952. Always considered a quiet, cooperative, well-behaved patient. On Feb. 5, 1952, she was placed on isoniazid and on May 9, 1952, she suddenly tried to commit suicide by jumping out of the window and was found to be acutely disturbed, dazed, apprehensive, and complaining of auditory hallucinations. At Bellevue, on May 10, 1952, she complained of auditory and visual hallucinations, talked, and prayed continuously. At Edgewood Division she was confused, tense, and fearful and denied hallucinations. Her disturbance had cleared up completely when she was examined on Aug. 1, 1952. Isoniazid was started in doses of 4 mg. per kilogram per day; improvement continued, and she was sent back to Sea View Hospital as recovered Oct. 9, 1952. At Sea View the dose of isoniazid was increased to 6 mg. per kilogram on Nov. 11, 1952. On April 20, 1953 she became very agitated, developed auditory and visual hallucinations, was destructive, denudative, talked incessantly, and refused food. She was returned to Edgewood, where the daily dose of isoniazid was reduced to 4 mg. per kilogram, and she was given 17 ECT's on a symptomatic basis. She showed improvement, gained 18 lb. (8.2 kg.), but died on July 28, 1953, of far-advanced tuberculosis with amyloid disease. It is probable that the amyloid disease which affected her kidneys resulted in an accumulation of isoniazid in the blood so that even 6 mg. was a toxic dose for her.

Iproniazid Psychosis: L. J., No. 48268, 36-year-old Negro woman, admitted Oct. 15, 1953. Continuously hospitalized in various city hospitals since February, 1950, because of far-advanced pulmonary tuberculosis with tuberculosis of the spine, for which she had had several spinal fusion operations. A complete paraplegia, due to transverse myelitis at T 5, had developed. In these hospitals she adjusted well. On Feb. 19, 1953, streptomycin and PAS were stopped after prolonged administration, and she was put on iproniazid, 3.5 mg. per kilogram per day. In August "nocturnal episodes of psychosis" were observed, and the drug was stopped. The psychotic symptoms disappeared and two weeks later the drug was started again with a smaller dosage, but one week later she developed "gross hallucinations" and the drug was stopped again. However, this time her hallucinations continued. She became threatening and more excited and was sent to Bellevue, where she had visual and auditory hallucinations, was confused and silly, and had grandiose ideas and inappropriate emotions. At Pilgrim State Hospital she continued to misidentify people, was disoriented, and assaultive, hallucinated continuously, and had grandiose delusions that she was the most beautiful girl in the world and was married to her orthopedic surgeon. This state continued until early in February, 1954, when rather abruptly she became pleasant, agreeable, and friendly and hallucinations were denied. However, she remains at present manneristic, rather silly and childish, and handles her paralysis by denial, saying, "just let me go home and I will be able to walk."

II. *Effects on Behavior and Affect.*—During the first few months of isoniazid administration, the drug was reserved for acutely sick patients. At that time there was repeated observation of euphoria, increased appetite and activity, even restless-

ness and agitation. Later, when the drug was administered to many patients without tuberculosis symptoms, euphoria was practically never seen, and restlessness, agitation, and increased tension was seen only in an occasional case and usually were easily managed with phenobarbital administration and disappeared if isoniazid was continued. Apparently, the euphoria was due to relief of tuberculosis symptoms and was absent when such symptoms were absent at the start of therapy.

III. *Epileptogenic Activity.*—A. Essential Epilepsy: Nineteen patients with epilepsy were placed on isoniazid treatment after the best dosage of the usual antiepileptic drugs had been determined. There was no observable effect on the number of seizures. One patient whose phenobarbital dose was cut in half during isoniazid therapy had two severe seizures and became so weak that he was placed on a critical status and isoniazid was dropped. Several of the patients who were in chronic clouded states or severely deteriorated brightened up and began to talk. A few became somewhat restless and more difficult to control but these effects were temporary.

B. Post-Traumatic Epilepsy: (Six cases): Of these patients, one with a post-traumatic psychosis who had never had convulsions, had a seizure four months after isoniazid was started; he was given diphenylhydantoin (Dilantin) and phenobarbital, and no more seizures occurred, although isoniazid was continued. One patient who was a heavy drinker had occasional seizures and a few periods of status epilepticus after a skull fracture in January, 1950, but had no seizures in this hospital after diphenylhydantoin and phenobarbital were started. However, one month after isoniazid was begun, he had three seizures in one hour and developed left hemiparesis, which lasted a half-hour. The other four patients all had seizures before administration of isoniazid and showed no increase in seizures, but two of these have had isoniazid only one month so far.

C. Symptomatic Epilepsy: 1. Four alcoholics with definite history of seizures while drinking ("Rum Fits") had no seizures on isoniazid therapy without antiepileptic drugs.

2. Many patients with cerebral arteriosclerosis without seizures were given isoniazid without seizures developing. However, one man aged 55, with a diagnosis of alcoholic psychosis but with evidence of generalized arteriosclerosis, who had never had any previous seizures had a severe fit on isoniazid therapy. The relationship to the drug is questionable.

D. Postlobotomy Seizures: 1. Four patients who had seizures after prefrontal lobotomy and who were well controlled with diphenylhydantoin and phenobarbital were given isoniazid; three showed no harmful effect. One patient, who had had a stormy postlobotomy course with prolonged stupor and temporary quadriplegia, subsequently developed epilepsy and, although easily controlled with diphenylhydantoin and phenobarbital, had one episode of severe status epilepticus when the drugs were inadvertently discontinued for a few days. One week after isoniazid was started he became agitated and hostile, and three days later he had a severe seizure with irregular pulse, muscle twitching, incontinence, mental dullness, and right Babinski sign, and looked so sick that he was placed on critical status. When isoniazid was discontinued, his condition cleared up in a few days, and he is very comfortable physically and has no seizures.

2. Two postlobotomy patients without seizures developed seizures after being placed on isoniazid treatment, and one had a temporary right hemiparesis subsequently. On antiepileptic drugs there were no more seizures, although isoniazid was continued.

3. To test the effect of isoniazid on postlobotomy patients, 25 female patients, all of whom had had lobotomies, on one ward were given isoniazid without streptomycin. Twenty had 5 mg. doses and 5 had 10 mg. doses per kilogram per day. Twenty-four of these patients were schizophrenics; one was an epileptic. The drugs were started on Feb. 8, 1954. None of these patients except the epileptic had previously had any seizures. One patient had a seizure on March 7, 1954, and diphenylhydantoin and phenobarbital were then started, and isoniazid was continued; there were no further seizures. Three patients, one on 10 mg. per kilogram and two on 5 mg. per kilogram became agitated and the isoniazid was discontinued, whereupon they quieted down. None of the other patients have shown any effects to date.

E. Meningitis: Five patients with tuberculous meningitis were treated with isoniazid; four treated with 4 mg. per kilogram had no seizures. One patient, A. C., No. 42826, a 19-year-old Negro woman had been treated for six weeks with streptomycin and PAS for advanced meningitis, with a spinal fluid protein of 4,500 mg. per 100 cc. The course was progressively downhill, and on April 19, 1952, when she was considered moribund, she was given isoniazid, 10 mg. per kilogram for one day and 5 mg. per kilogram for two days. She then went into status epilepticus; her temperature rose to 107.2 F., and she died in two hours. Postmortem examination showed miliary tuberculosis and tuberculous meningitis along the brain stem but no involvement of the convexity or of the gray or white matter of the cortex.

F. Effects of Isoniazid on Dosage of Electricity During ECT: There was no observable effect in many patients treated with ECT during isoniazid therapy. An attempt was made in a few patients to reduce the current at the time that isoniazid was started, with the result that petit mal occurred.

IV. *Neuropathy.*—Isoniazid therapy had to be discontinued in only two patients because of neuropathy. Both were without objective findings but had numerous complaints of numbness and burning and tingling of hands and feet. One patient was admitted with isoniazid psychosis and severe neuropathy caused by isoniazid, including wrist drop, atrophy of hand muscles, diminished sensation of the ulnar side of the forearm and hand and absence of deep tendon reflexes in the upper and lower extremities. Despite intensive vitamin therapy, there was very little improvement when he was discharged, five months later. Many alcoholics who were admitted with peripheral neuritis showed rapid recovery despite isoniazid administration. In three such cases vitamin therapy was not given, and their improvement appeared to be about as rapid as in the other cases. It was noted that the alcoholics receiving isoniazid showed remarkable appetites and increase in weight; it is suggested that the increased food intake included adequate vitamins without supplementation to cure the neuropathy.

SUMMARY AND CONCLUSIONS

In a group of 602 tuberculous mentally ill patients treated with isoniazid with a dose of 4 mg. per kilogram per day, the toxicity in comparison with the effectiveness of the drug was considered not to be serious. Only five patients who required isoniazid because of their tuberculosis had to have interruption of the drug because

of toxicity, three because of seizures, and two because of peripheral neuropathy. One patient who was moribund with advanced tuberculous meningitis and who was given a larger than normal dose, apparently died of convulsions induced by isoniazid.

Isoniazid has an aggravating effect on convulsive tendencies even in therapeutic dosage, especially in brain-damaged patients. That this effect is not so great as to contraindicate treatment of such patients was shown by administration to 25 patients who had had lobotomies. Antiepileptic drugs, especially phenobarbital, can usually, but not always, be depended on as antidotes. They were very effective in 18 of 19 patients with epilepsy who were given isoniazid.

Isoniazid even in normal dosage sometimes causes agitation, which usually can be readily managed by sedatives without discontinuation of the isoniazid. However, in excessive dosage it is capable of causing psychoses, as the toxicity is proportional to the plasma level; 16 patients with psychosis caused by isoniazid have been received at the Edgewood Division of Pilgrim State Hospital. In addition, iproniazid, which is far more toxic and which is used by few physicians, has caused the transfer to this hospital of nine psychotic patients. Twenty-five is a very small number when compared with the many thousands of patients who have been treated in New York City with these drugs from March, 1952, to March, 1954.

In excessive dosage isoniazid frequently causes peripheral neuropathy, but when normal therapeutic doses are used this effect is mild and does not contraindicate treatment in the presence of alcoholic neuropathy.

It does not appear to be dangerous to the aged, to arteriosclerotic patients, or to alcoholics. There is considerable individual variation in reactions to the drug, and some symptoms may appear early and disappear while the drug is continued, while others may appear only after prolonged administration. Hence large single doses do not give a reliable test of the long-term toxicity.

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SCHIZOPHRENIC-LIKE PSYCHOTIC REACTIONS WITH ADMINISTRATION OF ISONIAZID

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MANY COMPLICATIONS of the administration of isoniazid (isonicotinic acid hydrazide; and INH) and related compounds in man have been reported, but relatively few toxic psychoses have been described. We are reporting five cases seen at Charity Hospital of Louisiana, at New Orleans, in which such reactions developed while under treatment with isoniazid or iproniazid (IPH) in combination with other antituberculous drugs. These cases are similar to those previously reported in the literature,* and particularly to the three cases described in some detail.†

REPORT OF CASES

CASE 1.—A 27-year-old Negro woman was admitted to the tuberculosis unit with a small apical infiltration diagnosed as early pulmonary tuberculosis. The patient was treated with streptomycin, *p*-aminosalicylic acid (PAS), and isoniazid. After eight months of treatment the patient was transferred to the psychiatric unit, with a transfer diagnosis of "acute schizophrenic reaction, catatonic type." The patient had tried to jump from a window in an attempt to "get away from the isoniazid" which was "bad" for her.

On examination the patient was disoriented for person, place, and particularly time. Psychomotor activity was increased markedly. There was diffuse muscle jerking, most prominent in the hands and face, particularly about the eyes. Gradual improvement occurred with no specific therapy other than stopping of all medication and institution of routine custodial care. Two weeks after admission to the psychiatric unit she showed considerably less disorientation and only slightly increased psychomotor activity. Four weeks after discontinuation of isoniazid and the other drugs her appearance and performance were approximately the same as before the acute psychotic episode.

The earliest symptom which the patient later recalled was restlessness. Insomnia and inability to find sufficient outlet for her increased activity also distressed her. There was subjectively increased environmental awareness during this period, with increased sensitivity to auditory and visual stimuli. During the acute psychotic episode there was no insight, the patient explaining, "I'm here because my records got mixed up with someone else's." On remission she recalled only that she had been "nervous" when most ill. The patient gave no history of previous psychotic episodes. Although a seclusive, quiet person, she functioned adequately socially, and was well thought of in her work as a ward aide at the hospital.

CASE 2.—A 46-year-old Negro male laborer was admitted to the tuberculosis unit with severe pulmonary tuberculosis and a peripheral neuropathy in the lower extremities. Diagnostic work-up revealed no specific cause of the neuropathy, although from the history chronic malnu-

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* References 1 through 7.

† References 1, 5, and 7.

trition seemed likely. No mental changes were observed on admission, and the patient was able to give coherent present and past history. There has been no change in the neuropathy during the follow-up period of one year.

Three weeks after admission therapy was started with streptomycin, PAS, and isoniazid. The psychotic reaction appeared two weeks after therapy was initiated. The psychotic reaction became progressively severer for another two weeks, at which time isoniazid alone was discontinued. The initial impression was that of "possible drug psychosis." Review of the development of the psychosis revealed that the patient rapidly developed insomnia, restlessness, increased psychomotor activity, persecutory delusions, and vivid visual hallucinations. He acted upon his delusional and hallucinatory experiences and was in a constantly active, confused state during the acute psychotic episode. Three to four weeks after discontinuation of isoniazid these latter symptoms disappeared. Three months later he still had visual and auditory hallucinations, delusions, and loss of memory for recent and past events. One year later he still had signs suggestive of an organic mental syndrome, with marked disorientation for time, place, and person. Hallucinations are no longer described, but the patient has a great deal of difficulty in reporting his experiences.

Case 3.—A 31-year-old Negro woman was admitted to a nearby hospital with a diagnosis of pulmonary tuberculosis. She was treated with streptomycin, PAS, and isoniazid for a period of 10 months. The development of referential ideas and persecutory delusions made her increasingly uncomfortable, and she deserted the hospital. The patient reported that six months prior to the desertion she noted restlessness, insomnia, tremor of the extremities, dysesthesias, and increased sensitivity to light and sound. Referential idea of other patients talking about her developed at about the same time that a feeling of discouragement and incessant crying started. Three weeks after desertion (and stopping of all medication) she came to Charity Hospital and was admitted to the tuberculosis unit and restarted on streptomycin and PAS. Shortly after admission she was transferred to the psychiatric unit with a tentative diagnosis of "functional psychosis." On transfer she showed increased psychomotor activity, wringing of the hands, sobbing, and continual attempts to explain her referential ideas. There was disorganization of verbal productions, and motor activity was poorly coordinated. Although oriented for place, she was confused as to person and was disoriented for recent and past time. After eight weeks without isoniazid (the last five of which she was being treated with streptomycin and PAS) the delusions and referential ideas have decreased, auditory hallucinations have disappeared, and psychomotor activity is at a normal level. In spite of this improvement she is still quite disturbed and requires continued psychiatric ward care.

Case 4.—A 26-year-old Negro woman was admitted with a diagnosis of tuberculous salpingitis and localized peritonitis. She was treated with streptomycin, PAS, and isoniazid, with good clinical improvement. The patient apparently had a satisfactory adjustment prior to the emergence of the acute psychotic episode. Six months after admission, after several days of restlessness and insomnia, the patient suddenly misinterpreted a routine ward activity as a scene of a ward physician murdering an old man. A few hours later she heard a male voice from the ceiling warn her to leave the hospital or she would die. The patient recognized the hallucinatory nature of this voice but felt that it would be wise to leave "just in case it's true."

Psychiatric examination revealed that the patient was rational and cooperative, though suspicious and quite anxious. Mental status examination showed her to be oriented, but with a slight dyscalculia and confusion as to recent events. Rapid disappearance of the symptoms followed discontinuation of isoniazid, PAS, and streptomycin. Two weeks later the patient showed no evidence of psychosis, although anxiety and restlessness were present in a lessened degree.

Case 5.—The case of a 58-year-old Negro male bricklayer who had been unusually successful economically and socially in his community was diagnosed at another hospital as that of early pulmonary tuberculosis. He was treated with streptomycin, PAS, and iproniazid on an outpatient basis. Eight months after beginning this treatment irritability and increased anxiety gradually developed. Even though he was told to stop all medication at this time, he continued to take iproniazid until his admission to the psychiatric unit.

The patient was quite agitated by the time he was admitted, and he had been hiding in his home because of a persecutory delusion. On two occasions he had heard a "warning voice from above." The patient had attempted to conceal his hallucinatory and delusional experiences from his family, and later from his physician. On admission to the psychiatric unit he showed markedly

increased psychomotor activity, constant hand wringing, profuse sweating, and tachycardia. He showed gross muscle jerking, particularly in the face and hands, and tendon reflexes of low threshold. He was well oriented and cooperative in a fearful, ingratiating way. Two weeks after iproniazid was stopped, he showed marked improvement in psychomotor activity and denied his delusions. At this time he developed bizarre hypochondriacal complaints and was still referential. Two months later the patient was still anxious and suspicious, but he had lost much of his specific delusional material and was able to return home, though not to work.

Dosage levels of streptomycin, PAS, isoniazid, and iproniazid in all patients were within the usual therapeutic range. In all five patients neurologic examinations were normal except for the presence of gross muscle jerking and low-threshold tendon reflexes (and the peripheral neuropathy of the lower extremities noted in Case 2). Diagnostic work-up to exclude tuberculous meningitis as a factor in the psychotic picture was done when indicated and proved negative.

Aspects of the clinical picture which were prominent in our patients are the following:

1. Increased psychomotor activity. About one month before the acute psychosis each patient experienced insomnia, restlessness, and irritability. "I couldn't find enough to do with my hands," was the typical description. Later the patients noted a heightened awareness to environmental stimuli, particularly to light and sound. One patient attributed her psychosis, during the acute phase, to "the banging of garbage cans outside the window." Constant, purposeless, poorly coordinated muscular activity was outstanding during the acute phase. Gross muscle jerking resembling fasciculation was frequently noted in the hands, arms, face, and about the eyes. Thoughts and verbal productions were rapid and dissociated, paralleling the motor behavior.

2. Disorientation. This state was seen during and after the acute episode, varying from complete disorientation for time, place, and person to almost normal function in Case 5.

3. Insight. None of the patients seemed to recognize the prodromal signs as evidence of something untoward occurring. Only Patient 4 showed any insight into the acute delusional and hallucinatory experiences. Patients 1 and 3 referred to the acute psychotic episode simply as being "nervous." None could later recall details of the psychotic period. During improvement the patients did not associate with the other psychiatric patients, who were predominantly schizophrenic.

4. Projective-referential and illusory-hallucinatory experiences. In general these experiences were loosely organized in these patients and seemed to be a response, at least in part, to the heightened environmental awareness and to peripheral sensory disturbances. The referential ideas were interesting in that Patients 1, 3, and 4 wanted to leave the hospital. The first patient specifically blamed isoniazid for her predicament and wanted to "escape from it." Auditory hallucinations were present in all our patients, while only the second patient experienced visual hallucinations. The auditory hallucinations were poorly structured and frequently occurred in response to simple external stimuli. They were usually persecutory in content. The illusory experiences based upon routine ward happenings were vivid and frightening and often prompted impulsive behavior, such as attempts at defense or escape.

We feel it is important to note that a definite temporal sequence of events appeared in each patient. Quite early there was restlessness, insomnia, and increasing

anxiety. Concurrently the patients became aware of disturbing sensory changes, such as dysesthesias, numbness, and tingling, and became quite sensitive to auditory and visual stimuli. Later there appeared poorly structured referential and persecutory ideas which seemed to be related to the sensory experiences. Finally, the full-blown psychotic picture developed, incorporating not only the patient's previous personality pattern but also the more recent altered perceptions. On removal of the drugs the patient first and most consistently showed improvement in psychomotor agitation and the sensory complaints. Later, disorientation and confusion improved, and specific delusions and hallucinations diminished. Only much later, if at all, did anxiety and subtler affective changes improve.

The cases described in the literature in some detail ‡ are quite comparable to the five presented here. An abstract of these three cases and a reviewing of the five presented here suggest that the features emphasized above may constitute a recognizable clinical entity appearing in conjunction with the administration of these derivatives of isonicotinic acid. It seems unlikely that the other antituberculous drugs (streptomycin and PAS) have contributed to this picture.§

SUMMARY

Five cases are reported in which acute psychotic reactions occurred in association with the administration of isoniazid (or iproniazid) and streptomycin and PAS. These patients exhibited characteristic toxic-organic signs, in addition to a "schizophrenic-like" picture. Marked change, though not necessarily remission, occurred after the removal of isoniazid (or iproniazid) and the other antituberculous drugs. The characteristic symptoms appeared in a definite sequence, a feature which may be of significance in prediction of the possible occurrence of such acute psychotic reactions. This reaction seems most likely to occur in patients who already show prepsychotic adaptation. The syndrome as described here is consistent with the few cases reported in detail in the literature.

‡ References 1, 5, and 7.

§ Following the compilation of these five cases, the authors have identified two more cases in which acute toxic psychotic reactions occurred in patients receiving streptomycin, PAS, and isoniazid. These cases showed the same picture as those described here. In both cases there was a rapid remission of the psychotic signs following withdrawal of the isoniazid and continuation of streptomycin and PAS.

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FAMILIAL OCCURRENCE OF MIGRAINE HEADACHE

A Study of Heredity

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THE PATIENT with migraine headache commonly reports that some other member of his family has similar headaches. The migraine syndrome has long been considered familial, and some investigators have presented familial occurrences as evidence of its hereditary character. In 1873, Liveing, in his monograph on "megrim," commented on the frequent occurrence of migraine in the relatives of his "megrim" patients and observed that this disorder was often transmitted from parent to child, especially from a parent to those children who in other respects resembled him.[1] Christiansen was of the opinion that migraine is a dominant hereditary factor. This opinion was based on his observation of the very high percentage of his patients with severe migraine who had near relatives with migraine.[2] Ulrich studied 500 cases of migraine headache and believed that these patients all inherited a migraine constitution, and that circumstances such as alcohol, infection, fatigue, worry, and want do not cause migraine but precipitate it in such patients.[3] Fitz-Hugh suggested that migraine is a constitutional predisposition of the subject to react with headache to a variety of stimuli which in the nonmigrainous members of the population produce no such comparable effect.[4]

FAMILIAL OCCURRENCE OF MIGRAINE HEADACHE

Friedman studied a large group of clinic patients with migraine headache, 65% of whom gave a family history of migraine.* Balyeat stated that the factor of heredity in migraine was unquestioned and presented four detailed family trees showing the occurrence of migraine in two and three generations.[5] Graham, in a study of 46 patients with migraine headaches, reported that 80% of them gave a history of having relatives with migraine among the immediate family of siblings, parents, aunts, uncles, and grandparents.[6] Lennox found 61% of a group of 425 patients with migraine headache at the Boston City Hospital who were able to recall that a parent also had had attacks of "sick headache" of a similar nature.

From the New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College, and from the Department of Zoology and the Institute for the Study of Human Variation, Columbia University.

* Friedman, A. P.: Personal communication to the authors.

Lennox contrasted this group of 425 headache patients with a control group of nurses, medical students, and miscellaneous patients, among whom 11% were able to recall a parent with migraine headache.[7]

INCIDENCE OF MIGRAINE HEADACHE

In the consideration of a hereditary trait, the incidence of the trait in the general population is of interest and significance. In the present study it has not been attempted to collect new data on this aspect of migraine. However, Lennox,[7] on the basis of his own experience of finding an incidence of migraine of 5.4% in his control group of 1,000 and on the studies of Balyeat,[5] who found the incidence of migraine in different social groups varying from 3.7 to 13.5%, made a conservative estimate of 5% as the incidence of migraine in the general population. In a group of 10,000 young males Weider and associates [8] found an incidence of 9% of "frequent, severe, incapacitating headaches." Also, in a study of 15,000 patients in general practice, Grimes [9] found an incidence of 8% of migraine headache, whereas Fitz-Hugh,[4] in reviewing the private office records of 4,000 consecutive patients over 15 years, found an incidence of 22% of migraine headaches.

METHOD AND MATERIAL OF PRESENT STUDY

The hypothesis that migraine is not only familial but is also an inherited trait has been supported, and a definition of its mode of inheritance has been indicated by statistical analysis of family pedigrees obtained from 119 patients.

Basis of Selection of Patients for Study.—The patients selected for study had come to the New York Hospital with the complaint of severe headaches, recurring usually over many years. They were selected for this study on the basis of the following definition of migraine headache. Pain was usually unilateral in onset, sometimes becoming generalized before the end of the attack. Attacks were from less than an hour to several days in duration. The headache attacks were associated with anorexia, nausea, and vomiting, as well as with photophobia and mood changes. Some of the attacks were ushered in by scotomata, hemianopsia, unilateral paresthesia, or speech disorder. Some attacks were accompanied by vertigo, pallor, excessive sweating, and chilliness. These and a host of other features did not all occur with each attack. Some of the women patients had their headaches at the time of menstruation. Furthermore, in all instances the course of the headache was altered by ergotamine tartrate, and a family history of similar attacks was obtained from 83% of the 119 subjects.†

Because of their availability as residents of New York City and vicinity, 90 clinic patients of the New York Hospital were requested to come for an interview in regard to their migraine headaches. Ten of the request letters were returned, marked "Address Unknown"; 8 patients could not come for an interview; to 4 letters there was no reply, and 3 patients who came for interview were "discarded" because they had no knowledge of their families. Thus, 65 of the 119 patients studied had been treated for migraine headache during the past two years in an outpatient clinic of the New York Hospital.

† References 10 and 11.

There was another group, of 80 "private patients," who had at some time during the previous four years consulted one of us (H. G. W.) in regard to their migraine headaches. Because the majority of this group lived at such a distance from New

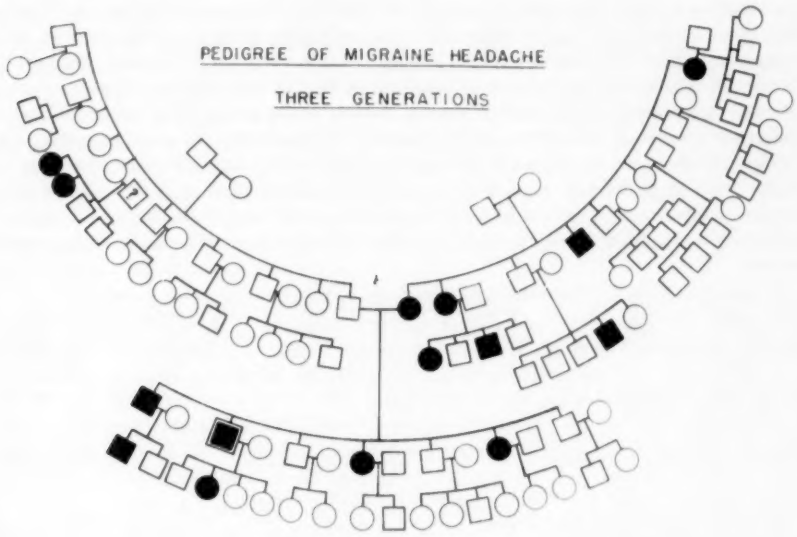

Figure 1

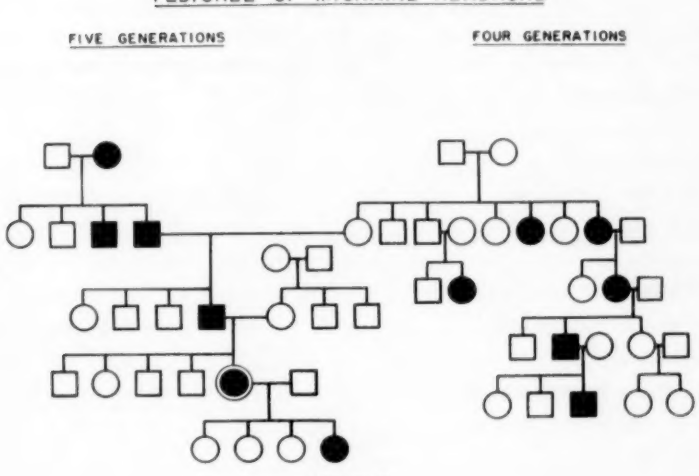

Figure 2

York that a personal interview did not seem feasible, information about their relatives was requested by means of a mailed questionnaire, which was accompanied by an explanatory letter. Fourteen of these were returned, marked "Address

Unknown," and to 12 there were no replies. In addition to answering the questionnaire, 25 of these "private patients" came for personal interviews. From the remaining 29 information was obtained from the questionnaire and letters.

Methods of Collecting Data.—Each one of the group of 65 clinic patients was interviewed in person for the purpose of questioning him, or her, about the occurrence of headaches similar to his, or hers, in other members of the family. First, each patient was asked the question, "Does anyone else in your family have migraine headaches similar to yours?" He was then asked to describe the relative's headache, or, if he could not do this, he was asked to get such a description from the relative himself, or from another member of the family. The number and sex of siblings and children of the patient, and of his parents and grandparents (where possible) were recorded. Each patient was urged to visit, or to communicate by telephone and letter with, any relative who might be able to extend or corroborate information about the occurrence of migraine in other members of the family. The authors interviewed 34 relatives of this group of 65 clinic patients, either in person or by telephone, in order to amplify information given by patients.

A family pedigree, as illustrated in Figures 1 and 2, was drawn for each patient.

As mentioned above, information about migraine headaches in the relatives of 54 "private patients" was obtained by means of a questionnaire and letters. The personal interview with 25 of this group was a means of amplifying and corroborating information given by questionnaire and by letter. A copy of the questionnaire follows:

Date.....

Name.....

MIGRAINE HEADACHE QUESTIONNAIRE

Will you recall to the best of your ability any members of your family who have, or have had, migraine headaches? Please list *all* of your relatives, indicating those who have had, or have, the headaches.

Mother.....

Father.....

Brothers: Total number..... How many with migraine headaches?.....

Sisters: Total number..... " " " " " .....

Mother's mother.....

Mother's father.....

Mother's sisters: Total number..... with migraine headaches?.....

Mother's brothers: " " ..... " " " .....

Father's mother.....

Father's father.....

Father's sisters: Total number..... with migraine headaches?.....

Father's brothers: " " ..... " " " .....

Cousins on your mother's side: #..... " " " .....

Cousins on your father's side: #..... " " " .....

Your children.....

Your spouse.....

In addition, can you or your parents recall, or can you obtain information about, migraine headaches occurring in great-grandparents?

Whenever possible, information about the occurrence of migraine in the family of the patient's spouse was also obtained.

These 119 patients gave evidence that they had made careful effort to verify their statements about their relatives having migraine headaches. In 34 instances, as mentioned above, the authors were able to interview siblings, children, or parents of patients, either in person or by telephone, to amplify the description of headaches and make it certain that these relatives actually had migraine headaches. Many patients made visits and telephone calls or wrote letters of inquiry to relatives who lived at a distance. Thus it was possible to obtain information, from surviving relatives' descriptions, of the occurrence of migraine headache in three, four, and even five, generations of a family. One patient was in possession of the diary of her great-grandmother, who had faithfully recorded her recurrent incapacitating migraine attacks. There were 12 men and 2 women physicians in the group, who took special care to verify the occurrence of migraine headaches in their relatives and to construct extensive family pedigrees. One woman wrote to a surviving grandmother in Ireland, whom she had never seen, for information about her father's numerous siblings. A male patient, whose father and mother had 10 and 5 siblings, respectively, made many family visits and carried on correspondence for several months with aunts, uncles, and cousins, scattered from Maine to California, until the patient was satisfied that he had assembled a correct pedigree.

Comment on Reliability: In dealing with these human clinical data it was recognized that genetic controls were lacking. It was appreciated that an identical hereditary equipment might give expression to headache in one environment and not in another. Also, the mere fact of having one or both parents with migraine may be an environmental influence conducive to migraine in the offspring. No opportunity has yet been offered to test the occurrence of migraine in such offspring reared by foster parents without migraine.

Furthermore, the method of obtaining information about the occurrence of migraine headache in other members of the family, by asking patients to recall such illness in relatives both temporally and spatially distant, may be seriously unreliable, especially since the complaint of pain in the head from a variety of causes can be elicited from approximately 85% of the population. However, there is an immediate advantage in terms of the probable reliability of data obtained from persons with migraine headache. Such persons are usually characterized by their perfectionism, their excessive feelings of responsibility, and their need to perform with exactitude and meticulous attention to detail.‡

DESCRIPTION OF DATA

Of the group of 119 propositi (i. e., patient informers), 48 were males and 71 were females. Twelve men and 2 women were physicians. All the men were employed, and approximately half of the women. The remainder of the women reported themselves as housewives. Ages of the group ranged from 16 to 65 years, distributed as follows:

Age Group	No. of Patients
16 to 25	7
26 to 30	12
31 to 35	13
36 to 40	13
41 to 45	22
46 to 50	22
51 to 55	17
56 to 60	9
61 to 65	4

‡ References 3, 7, and 11.

Table 1

PEDIGREES ARE FROM 119 MIGRAINE PATIENTS 48 MALES AND 71 FEMALES WHO HAD 343 RELATIVES WITH MIGRAINE
20 PATIENTS HAD NO MIGRAINE RELATIVES
66 PATIENTS HAD 1 – 3 MIGRAINE RELATIVES
22 PATIENTS HAD 4 – 7 MIGRAINE RELATIVES
11 PATIENTS HAD 8 – 19 MIGRAINE RELATIVES

Table 2

OCCURRENCE OF MIGRAINE IN GENERATIONS OF THE PEDIGREES			
GENERATIONS	MALES	FEMALES	TOTALS
1	9	15	24
2	20	23	43
3	13	27	40
4	4	5	9
5	2	1	3

Sixty-one patients remembered having migraine headaches in childhood or in adolescence.

In the families of the 119 propositi, there were 343 instances of the migraine phenotype (i. e., persons manifesting migraine headache). Table 1 shows the following distribution of relatives with migraine: Twenty patients had no relatives with migraine; 66 patients from 1 to 3 relatives with migraine; 22 patients had from 4 to 7 relatives with migraine, and 11 patients had from 8 to 19 relatives with migraine. In the families in which these instances of migraine occurred there was a total of 832 offspring.

There were reported to be relatives with migraine in as many as five generations of 3 of these families, in four generations of 9 families, and in three genera-

Table 3

OCCURRENCE OF MIGRAINE

IN THE CHILDREN OF FAMILIES HAVING MEMBERS WITH MIGRAINE

CHILDREN	PARENTS HAVING MIGRAINE		
	NO PARENT	ONE PARENT	BOTH PARENTS
TOTAL NUMBER OF CHILDREN	265	502	65
NUMBER WITH MIGRAINE	76	222	45
PERCENT WITH MIGRAINE	28.6	44.2	69.2

tions of 40 families. A summary of the occurrence of migraine in the generations of the pedigrees is shown in Table 2, and examples are illustrated in Figures 1 and 2.

Figure 1 is the family pedigree of a male propositus, a physician, aged 65, who was able to verify to his satisfaction the diagnosis of migraine headaches in 14 of his relatives, distributed among three generations. Figure 2 is the pedigree of a female propositus, aged 42, who had 11 relatives with migraine, distributed among five generations.

From examination of Figures 1 and 2, the number of offspring in families having members with migraine can be counted, and those offspring having parents with migraine can be counted separately from those whose parents do not have migraine; also, the total number of offspring having migraine can be counted. Such counts were made for each pedigree of the 119 propositi. Table 3 summarizes the incidence of migraine headaches among the 832 offspring in the families having

members with migraine. Thus, among 265 of these offspring having neither parent with migraine, 76, or 28.6%, had migraine; of 502 having one parent with migraine, 222, or 44.2%, had migraine, and of the 65 offspring both of whose parents were affected, 45, or 69.2%, had migraine headaches.

Comment.—Data showing the occurrence of migraine headaches in families for two, three, or more generations have, to a number of investigators in the past, strongly suggested the hereditary nature of the migraine trait. More suggestive evidence of the hereditary nature of the migraine trait can be seen, however, in the summarized data presented in Table 3, especially because it is evident that the probability of migraine headache in offspring increases with the number of parents affected. Therefore, in order to establish the significance of these data as regards

Table 4

MEASURE OF INHERITANCE

(INCLUDES OFFSPRING WHERE PROPOSITUS IS ONLY AFFECTED PERSON IN FAMILY)

MIGRAINE:		NO PARENT	ONE PARENT	BOTH PARENTS	TOTALS
OFFSPRING AFFECTED	OBSERVED	76	222	45	343
	EXPECTED	109	207	27	
	DIFFERENCE	−33	+15	+18	
OFFSPRING NON-AFFECTED	OBSERVED	189	280	20	489
	EXPECTED	156	295	38	
	DIFFERENCE	+33	−15	−18	
TOTALS		265	502	65	832

$$\text{CHI SQUARE} = \lesssim \frac{(\text{OBSERVED} - \text{EXPECTED})^2}{\text{EXPECTED}} = 39.35$$

(WITH 2 DF) $P = < 0.001$

THEREFORE THE TRAIT OF MIGRAINE IS INHERITED

the hereditary aspect of the migraine trait, genetic concepts of heredity and mode of inheritance have been applied.

APPLICATION OF GENETIC CONCEPTS AND MODE OF INHERITANCE

It was assumed that the trait of migraine headache was not inherited. A χ^2 test of homogeneity was applied to the differences between the actually observed and the theoretically expected frequencies of migraine in the 832 offspring in the families of the 119 propositi. This computation revealed a probability of less than one chance in a thousand that such deviations would occur if the assumption of no inheritance were true (Table 4). Therefore, stated positively, it is highly probable that migraine is inherited. Furthermore, it is reasonable to assume that migraine is due to a recessive gene whose penetrance is approximately 70%. Penetrance indicates the ability of a gene to be sufficiently active in the development of an organism so as to show its effect in the final phenotype.

The figure of 70% penetrance was obtained from the fact that of the 65 offspring of parents both of whom had migraine, only 45, or 69.2%, had headaches. On the assumption that migraine is due to a recessive gene, 100% penetrance would result in 100% affected offspring when both parents have migraine.

If migraine were dependent on a recessive gene with 100% penetrance, we should expect 25% of the offspring of two heterozygous parents to show the trait. Since penetrance is indicated to be not complete, the figure for offspring showing the trait should be 70% of 25%, or 17.3%.

In order to rule out possible accidents, such as phenocopies, pedigrees with one affected person only were discarded. Data from families of propositi were corrected for bias, using the method of Haldane.[12] Migraine was found in 15.4% of the siblings of the propositi and in 37% of the siblings of affected persons who were not propositi.

Two main sources of error in these data are reflected in the figure of 15.4% for frequency of migraine in the siblings of propositi and that of 37% for frequency in the siblings of nonpropositi. Propositus data are low because the age of onset is relatively late—in general, after the age of 20 for about half of those who have migraine. On the other hand, a bias in the opposite direction is that the nonpropositus data are too high because all headaches in older relatives remembered by propositi may not have been migraine, although effort was made, as described above, to exclude these by insistence on careful descriptive data.

When analysis was carried further, combining the calculations for propositi and nonpropositi, weighting by the sample size, and correcting for penetrance, the proportion of affected offspring from a mating of two heterozygotes turned out to be 29%. On the basis of calculations of the variance of the estimate, this is not significantly different from the expected ratio of 25% manifestation of a recessive gene.

COMMENT

The alternate possibility exists that migraine headache is due to a dominant gene with partial penetrance, rather than to a recessive one. The difficulty of such a hypothesis is that it is essentially untestable. Such an assumption can be made for every human trait without inspection of the data, since a dominant trait with partial penetrance can explain any sort of data. Such a possibility must, then, be left open, it being realized at the same time that it is an unfruitful and untestable hypothesis.

SUMMARY

Highly significant evidence has been offered demonstrating the hereditary character of migraine and permitting one further to assume correctly that the inheritance of the migraine headache trait is through a recessive gene with a penetrance of approximately 70%.

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GREAT OCCIPITAL-TRIGEMINUS SYNDROME AS REVEALED BY INDUCTION OF BLOCK

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THIS TRIPARTITE syndrome presents symptoms (1) confined to the distribution of the great occipital nerve, (2) shared by the trigeminus, or (3) shown by the trigeminus alone, as a nociceptor to passive stimulation by the vulnerable great occipital nerve.

TABLE 1.—*Incidence of Syndrome*

Number of patients	100
Males	34
Females	66
Right side	32
Left side	39
Bilateral	29

TABLE 2.—*Great Occipital Neuritis Only*

Wincing spot over great occipital nerve	38
Pain from neck to coronal suture	38
Pain caused or made worse by exposure to draft	12
Pain on combing or brushing hair	17
Pain on pressure of head on pillow or hard surface	4
Sensation of pressure atop head	1
Click in occipital region on rotating head	2
Tender spot over nerve (volunteered by patient)	2
Stiff neck, relieved by block	16
Pain worsened by moving either arm	1
Simultaneous involvement of 3d occipital	7
Numbness (when examined for) after block	
Present at end of 6 mo	2
Present at end of 12 mo	2
Recurrence	7

In every case alcohol block (Fig. 1) relieved all symptoms. Pinprick verification of numbness was made in all cases; it presaged relief lasting 6 to 12 months, permanent relief being more frequent than recurrence.

At times the needle piercing the great occipital nerve produced pain radiating to the homolateral supraorbital notch (Fig. 1; Table 3).

Most of the items in Table 3, together with relief of all symptoms on block of the great occipital nerve, suggest a functioning contact between the great occipital nerve and the trigeminus. According to Ramón y Cajal,* only those fibers derived from the ophthalmic division of the trigeminus reach the lowest level (C 2) of the trigeminospinal tract (Fig. 1*A*), where, by collaterals and terminal branches, they

* Ramón y Cajal, cited by Kuntz.[1]

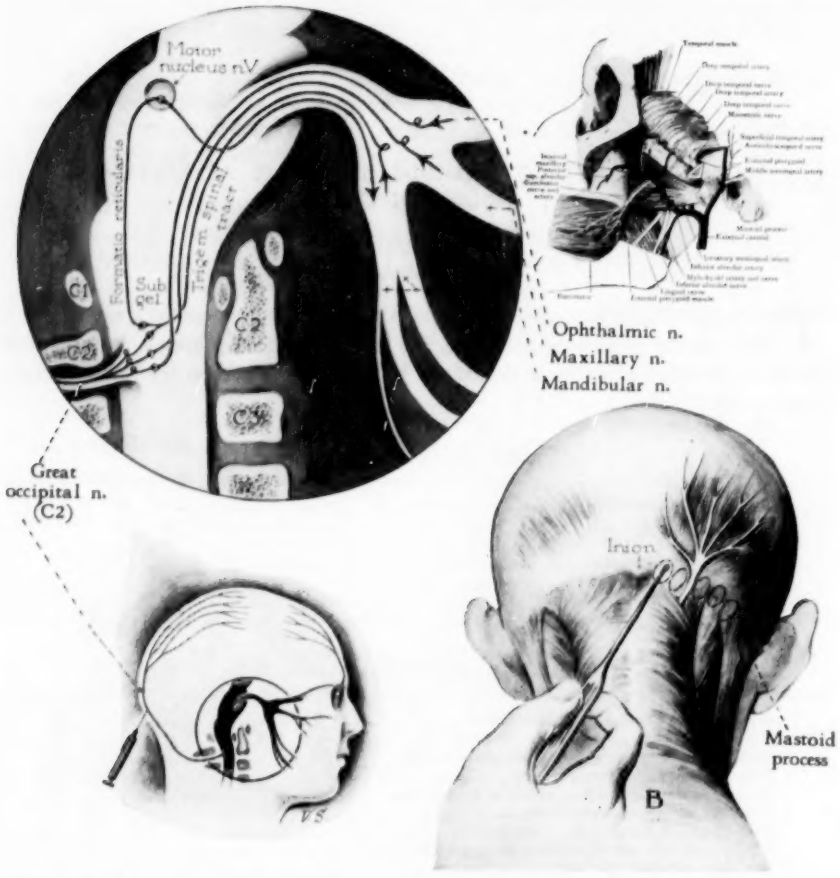

Fig. 1.—Schema (upper left) showing author's conception, based upon the clinical findings, of the synapse between the great occipital and the trigeminal nerves. For simplicity the probable tract intercalations are not delineated. Note that the fibers from the three divisions of the trigeminus descending in the trigeminospinal tract reach their respective levels in inverse order, the lowest being the ophthalmic, fibers of which terminate at C2, and therefore receive the first impulses from the great occipital nerve. Note the reflex connection from the lower part of the nucleus of the trigeminospinal tract to the motor nucleus of the trigeminal nerve; thus is explained the instant reversal of masticatory spasm upon alcohol block of the great occipital nerve. The inset (*B*) shows a small (grape-seed size bowl) curette searching for the wincing tenderness, which, with pressure or needle radiations, betrays the site of the great occipital nerve. Also shown (lower left) is the upward and forward direction of the needle injecting above the superior nuchal line. The needle should not be passed too deep, since at this level the nerve rests in the fat underlying the thick skin of the scalp. Also entering into this picture is the well-established antidromic course of sensory impulses.

Fig. 2 (upper right).—Dissection of the infratemporal fossa. Note the buccinator nerve emerging between the two heads of the lateral (external) pterygoid muscle, to which it distributes branches, as well as to the temporal muscle and on the lateral surface of the buccinator muscle unites with branches of the facial nerve to form the buccal plexus, from which branches are distributed to the mucous membrane and the skin of the cheek. (Cunningham, D. J.: Manual of Practical Anatomy, Ed. 11, London, Oxford University Press, 1948, Fig. 65, p. 163.)

end in the inferior portions of the nucleus of this tract and in the substantia gelatinosa in the upper segments of the spinal cord. Fibers derived from the maxillary nerve terminate at somewhat higher levels, while those from the mandibular nerve terminate in the superior portions of the nucleus of the trigeminospinal tract, higher than shown in the sketch (upper left). Thus, impulses from the great occipital nerve

TABLE 3.—*Great Occipital-Trigeminus Syndrome*

Occipito-ophthalmic radiation to supraorbital notch, nerve, "frontal sinus," eyeball	28
Radiation to maxillary division ("antrum," 16)	18
Pain in upper teeth, relieved by block	2
Radiation to mandibular division (auriculotemporal, 10)	12
Tenseness of masticatory muscles	1
Complicated by spastic tic (convulsive)	1
Onset with throbbing in nape, radiating forward to forehead	1
Throbbing in entire face during acute attack	1
Pressure at supraorbital notch, causing pins-and-needles sensation to radiate to coronal suture	1
Pressure at infraorbital foramen, causing severe pain in nape	1
Pain in eye caused by rubbing nape	1
Relief when patient massages nape	1
Bilateral headache relieved by unilateral block	3
Pain radiating to opposite great occipital nerve	1
Symptoms bilateral (unilateral lesion)	1
Sphenopalatine ganglion cocainized elsewhere; no relief	1

TABLE 4.—*Symptoms Manifested by Trigeminus Alone, as a Nociceptor to Passive Stimulation by Vulnerable Great Occipital Nerve*

I. Zoster ophthalmicus	
No. of cases	3
Males	2
Acute (3 days)	1
Subacute (5 wk.)	1
Chronic (2 yr.)	1
Left side	3
Dimness of vision	2
Conjunctiva inflamed	1
Sudden eruption of itching vesicles on forehead	2
Hyperesthesia, rubor, and calor over forehead	2
Ulcer, involving entire left area of forehead (5 wk.)	1
Postzoster scars on forehead (2 yr.)	1
Pain in distribution of supraorbital nerve	3
Postzoster neuritis of supraorbital nerve (2 yr.)	1
Paresthesia in infraorbital distribution (2 yr.)	1
II. Painful spasms of lateral pterygoid muscle	
No. of cases	3
Females	2
Right side	3
Excruciating pain on physiologic use of jaw	3
Variously located "trigger" zones (chiefly in buccal area)	3
Sensitive frontal scalp	2

would reach, first, the ophthalmic division; next, the maxillary, and, last, the mandibular. This concept is supported by the diminishing number of cases represented by the three divisions (from above downward in Table 3).

In Group I, alcohol block of the great occipital nerve immediately relieved the pain in all cases and scotched the trophic (sympathicotonic?) factor in the acute and

subacute cases, in which healing was completed within a week or 10 days; the chronic case also required alcohol block of the supraorbital nerve for postzoster neuritis.

In Group II, a nonagenarian was treated in the throes of an acute attack of painful pterygoid spasm, which was instantly checked by alcohol blocking of the great occipital nerve. In no case did the attacks recur during the duration of the alcohol block. Group I exemplifies stimulation of a sensory, and Group II stimulation of the motor, element of the trigeminus by the nociferous great occipital nerve.

COMMENT

Here, clinical research seems to have stolen a march on descriptive anatomy in pointing out the likelihood of a functioning contact between the great occipital nerve and the trigeminus, as suggested in the legend for Figure 1. Note also the reflex connection with the motor nucleus of the trigeminus, accounting for the spasm of the lateral pterygoid squeezing the buccinator nerve in transit (Fig. *2*), just as a spastic psoas squeezes the lumbar plexus. Procainization of the pterygoid relaxes the muscle, decompresses the traversing buccinator and juxtaposed nerves, and checks the spasm just as promptly and effectively, though less lastingly, as does blocking of the great occipital nerve itself. This conception of the reflex connection ascending to the motor nucleus of cranial nerve V (Fig. 1*A*) is approved by Dr. Albert Kuntz, of St. Louis.†

Two hauntingly moot questions occur: Why does the trigeminospinal tract descend to the second cervical level if not to establish functional contact at that level? Does the great occipital nerve, once inflamed, undergo complete resolution or become vulnerable as a locus minoris resistentiae and revert to the status of a nociferous nidus, periodically to irritate the trigeminus? Thus, its inciting role lessens in activity from the first to the third division of the syndrome, as described at the beginning of this paper. Should this conception be confirmed, posterior rhizotomy [2] would be indicated in persistent recurrences. The rationale of Sjöqvist's trigeminospinal tractotomy may well be the inclusion in the division of the reflex connection to the motor nucleus of cranial nerve V, shown in Figure 1*A*.

Approaching the coronal suture, the great occipital nerves ramify, just beneath the skin, to form from ear to ear a brush of antennae (Fig. 1, lower left) receptive to frigorific noci.‡

With threshold of the sympathetic nucleus depressed to admit noci, the sympathicotonic influence enters and effects ciliary spasm (via the ciliary ganglion) and other ocular disturbances (Fig. 3), which may culminate in zoster ophthalmicus (Table 4). Other symptoms are stuffy nose and pharynx sicca (via palatine nerves descending from the sphenopalatine ganglion)—additional tributes to the supremacy of catabolic sympathetic over anabolic parasympathetic action. So, too, in my recent article,[3] causalgia and other sympathicotonic symptoms were reported to vanish from the upper extremity after alcohol block of the suprascapular nerve. By

† Personal communication to the author.

‡ An arrangement somewhat resembling that of the lateral femoral cutaneous nerve when inflamed (meralgia paresthetica) with irritation of the lumbar plexus, each nerve traversing a dense iter.

sympatholysis, great occipital nerve block forthwith results in clarification of print, detumescence of the stuffy nose (in 100% of cases, barring those of spur and polyp), and bedewing of the pharynx. This clinical observation caused me to alter the first division in Table 3 from occipitofrontal to occipito-ophthalmic. Likewise, the prodromes of a "head cold"—the sensation of chilled feathers in the scalp, the ready sneeze, the stuffy nose (sympathicotonic noci reaching the nasal membranes via posterior lateral nasal nerves passing forward from the sphenopalatine ganglion to erectile tissue on the conchae), etc.—may be explained by paresthesia produced by stimulation of the great occipital nerve by frigorific noci, and, in turn, stimulating the sympathetic fibers. Similarly, is the occasionally concomitant facial tic § due to irritation of the buccal plexus in pterygoid compression of the buccinator nerve, and is Sluder's sphenopalatine ganglion syndrome due to irritation of this ganglion transmitted by the sphenopalatine nerves descending from the stimulated maxillary division?

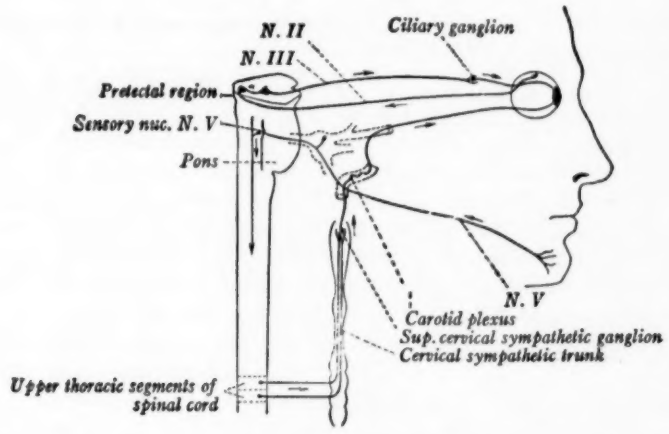

Fig. 3.—Pupillary reflex arcs. Note ceptors on chin for the pupillary-skin reflex, and on retina for the light. Arrow descending the cord reaches T2 via the trigeminospinal tract and the fasciculus proprius. (Ranson, S. W.: Anatomy of the Nervous System: Its Development and Function, revised by Sam L. Clark, Ed. 8, Philadelphia, W. B. Saunders Company, 1947, Fig. 266, p. 339.)

Sympatholysis sequential to isosegmental somatic nerve block by alcohol usually proves to be satisfactorily durable.

Figure 3 serves as a pattern of the paths taken by somatosympathetic reflex arcs in the cranial region.

Interpretation of the results of procainization of the lateral pterygoid muscle is equivocal, it is true; if, however, the buccal mucosa retains its epicritic sensation, the buccinator nerve has been decompressed, and not incidentally blocked. This nerve with its overflow is apparently the source of the so-called "trigger zones."

§ The symptom to which the designation tic douloureux was first applied.

Finally, it is of much interest to note that many years ago Sir Frederick Treves [4] foreshadowed this paper in the following words:

To understand the various pains which are so frequently referred to areas supplied by the great fifth nerve—neuralgias, headaches, migraine etc.—it is necessary to realize some of the central connections of the sensory nucleus in which its afferent fibers terminate. This nucleus extends to the lower part of the medulla oblongata and is continuous with the posterior horn of the spinal grey matter in which the sensory fibers of the occipital and other cervical nerves end.

SUMMARY

A tripartite great occipital-trigeminus syndrome as revealed and relieved by induction of block is described. By the deductive method, functioning contact between the great occipital nerve and the trigeminus looms out of the anatomic fog. Analyses of the 100 cases are included (Tables 1 to 4).

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PROTEOLYTIC ENZYME SYSTEM IN SEXUAL DEVIATES

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AND
ROBERT LIECHTI, B.S.
LOS ANGELES

AS PART of a research program on sexual deviation,* a comparative study of several biochemical measures was made in an attempt to define or differentiate subgroups within a total population of hospitalized male sex offenders. This paper reports the results obtained with one of these measures, a compound or compounds present in blood sera which can be quantitatively evaluated by its inhibitory action on the milk-clotting properties of rennin enzyme.

The metabolic significance of rennin inhibitor has not yet been fully explored. Concentrations in blood serum vary with age and with certain conditions of health and disease. High levels are normally found in children, adolescents, and women during pregnancy.[1] Elevations of rennin inhibitor are frequently observed [2] in hypertension and asthma and during convalescent periods following acute illness and fractures. In malignant disease [3] concentrations of rennin inhibitor tend to drop under conditions of rapid tumor growth, rising to high levels as growth is controlled or when spontaneous regression occurs. On the basis of these findings it has been speculated † that elevated rennin inhibitor levels in human blood sera may reflect heightened anabolic activity.

Jacobs and Tempereau [4] have reported high levels in adult schizophrenics (primarily catatonics) who show particularly weak ego defenses, low frustration tolerance, and fragmented behavior under stress situations ordinarily expected to arouse hostile reactions.

In a preliminary survey [5] the rennin inhibitor levels of 95 sex offenders confined at Metropolitan State Hospital for treatment under the California Sex Psychopath Act were found to be significantly higher than those obtained from a control group of 141 students, physicians, and other healthy subjects within the same age range. Since the stress of arrest, conviction, and incarceration may have accounted in part for elevations found in the sex offender group, a new study was formulated in which the factor of institutionalization could be held constant.[6] In order to control this factor, two subgroups from the population of hospitalized sex offenders were studied.

* This project, conducted by the University of California School of Medicine at Los Angeles, in cooperation with Metropolitan State Hospital, Norwalk, was part of a larger study on sexual deviation sponsored by the California State Legislature.

† West, P. M.: Personal communication to the authors.

Within the group of men convicted of sex offenses and referred to the hospital for observation and diagnosis, there is considerable variation in terms of personality organization, general life adjustment, and degree of emotional illness. Variation is also evident in the number and type of previous offenses and associated cultural and situational factors. The records of some offenders, for example, reveal little or no abnormal sexual behavior except in the presence of unusual circumstances, and their offenses often appear to result primarily from the pressure of situational or cultural factors. On the other hand, some offenders manifest neurotic or psychopathic personality features which seem to dispose them to repeated sex offenses in the absence of situational provocation and without regard to consequences. These groups could be conceived of as extremes of the hospitalized sex offender population ranged on a dimension of personality adjustment.

The present study was formulated to test the hypothesis that these subgroups, termed for purposes of this experiment "minor sex deviates" and "major sex deviates," are distinguishable on the basis of differences in their physiological reactions to stress, as these reactions are reflected in the level of rennin inhibitor present in the blood serum.

Subjects used in this study were men convicted of some sex offense and committed to Metropolitan State Hospital for a 90-day period of observation and diagnosis. Their ages ranged from 22 to 60 years, with a mean age of 34. Nearly all were native-born white men. As a group their intelligence distribution was fairly normal and the number of school grades completed approximated the national average. Offenses leading to their conviction included indecent exposure, child molestation, rape, and homosexual contacts with minors. Approximately 60% had records of previous sex offenses. None had received psychotherapy at the time of the experiment.

PROCEDURE AND METHOD

In order to test the hypothesis of this study, the subjects were first divided into the two categories of "minor" and "major" sex deviates. This division was derived from independent ratings by members of the clinical staff of psychiatrists and psychologists of the hospital. All psychiatrists and psychologists utilized as raters in this study had been actively involved in the diagnosis and/or treatment of sexual psychopaths over a period of not less than two years at the Metropolitan State Hospital. In addition, the psychiatrist raters have all served at various times as examiners for sexual psychopathy appointed by the Superior Court of California.‡ Ratings were procured on each patient immediately after a staff review conducted for the purpose of making recommendations to the court as to further disposition of the cases. Each sex offender was rated on a seven-point scale of degree of personality deviation, with scale steps ranging from "very extremely deviated" to "little or no deviation."

Raters were asked to assign ratings on the basis of their judgment as to the severity of the personality maladjustment presumed to be linked to the sexual behavior of the offender. Level of agreement between raters was determined by a method suggested by Garrett and Zubin.[7] The resulting interrater reliability correlation (r') reached 0.66, a satisfactory level of agreement between raters in view of the difficulty of the rating task. This made it possible to average the various ratings for each sex offender and to utilize the resulting mean rating for allocation of the subjects to positions along the rating scale.

‡ Robert E. Wyers, M.D., Hyman Tucker, M.D., John A. Mitchell, M.D., Dayrel D. Smith, M.D., David K. Geddes, M.D., and Maxwell Gage, M.D., psychiatrists, and Trent E. Bessent, Ph.D., Charles Cabeen, M.A., and Steven K. Abe, M.A., psychologists, served as raters for this study.

By this method, composite ratings were obtained for 100 cases. The distribution of these subjects along the rating scale was as follows:

Average Rating	No. of Cases
5.0-5.9	8
4.0-4.9	28
3.0-3.9	26
2.0-2.9	17
1.0-1.9	21

Subjects with ratings below 3 were designated minor sex deviates. The higher-rating group, with ratings of 3 or more, may be considered an experimental group for comparison with a control group of low-ranking offenders.

Determinations of rennin inhibitor concentration in blood serum were made on each subject under both stress-producing and comparatively normal conditions. The stress condition was defined as the patient's appearance at diagnostic staff. This procedure represents a stressful event in that the staff decision determines in large part whether the sex offender shall be confined to the hospital on indeterminate commitment for care and treatment. Consequently, the level of ego involvement and anxiety is high for most patients in the staff situation.

Rennin inhibitor determinations by the method suggested by West and Hilliard [2] were made immediately prior to the staff appearance of each subject. Similar determinations were made one week prior to and one week following staff appearance, when tension was lower. Thus, it was possible to compare major and minor offender groups in terms of measures taken under both heightened and lowered stress conditions.

Inasmuch as rennin inhibitor levels are influenced by age and certain disease states, no subject was included in the study whose age was less than 22 or more than 60 years, and no subject was included whose chest x-ray, white blood cell count, or sedimentation rate suggested the presence of disease.

RESULTS

In order to assess the reliability of results obtained, the sample of 100 cases was divided into two subsamples of 50 cases each. This division was made on the basis of date of staff appearance, so that the first 50 subjects appearing consecutively at diagnostic staff formed Sample I, which included 21 minor and 29 major deviates; while Sample II, the second group of 50 subjects, included 17 minor and 33 major deviates.

Minor and major groups were first compared on the basis of change *versus* no change in rennin inhibitor concentrations under the stress of staff appearance. It was found that some subjects showed an elevation of rennin inhibitor, while others showed no change or a decrease under this stress situation. Since no consistent pattern of directional change was evident in either minor or major group, the comparison of these groups was based solely on the presence or absence of change in inhibitor level on the day of staff appearance.

Figure 1 compares the minor and major groups in terms of this variable.

Stress-nonstress ratios ranging from 0.90 to 1.10 are classified as no change. Ratios outside this range are considered to indicate a change under stress. The subsample differences tested by χ^2 are consistent in direction and close to statistical significance (P levels of 0.03 and 0.08). When Subsamples I and II are combined, the probability of chance occurrence for the differences obtained is less than 1 in 1,000. It therefore appears possible under the conditions specified for the experiment to distinguish minor from major sex offender groups on the basis of variability of rennin inhibitor levels, with minor offenders showing less change under stress than major offenders.

A comparison was then made of the mean rennin inhibitor levels of major and minor deviates. These mean values were obtained by averaging all the determinations taken on each subject under both stress and nonstress conditions. West § considers that the normal range of adult values falls between 8 and 12 units. A comparison of the numbers of major and minor deviates falling within and outside these limits is shown in Figure 2.

Almost three-quarters of the values for the minor deviates fell between 8 and 12 units, while nearly two-thirds of the major deviate values fell outside this range. This difference between minor and major groups when tested by χ^2 is significant at the 0.002 level of probability and is consistent for both subsamples, as well as

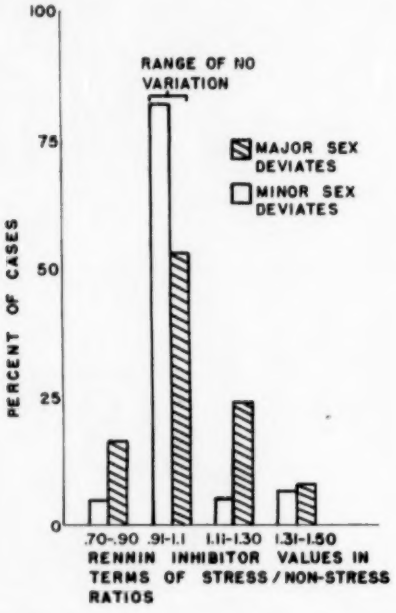

Fig. 1.—Comparison of minor and major sex deviates in terms of change in rennin inhibitor level as a function of stress. Abscissa values represent ratios of nonstress rennin inhibitor levels divided by values determined when the subjects were facing a stressful situation.

for the combined groups. Age variation, a factor known to influence rennin inhibitor level, does not account for this difference, since the mean age values for major and minor offenders differed by less than one year. The mean age of the major offenders is 36.0 years, and that of the minor offenders is 36.5 years.

A further study of this relationship was made by comparing the rennin inhibitor values for the 20 subjects having the highest sexual deviation ratings with the 20 having the lowest ratings. Differences obtained by this comparison were more striking. Only 3, or 15%, of the 20 minor deviates had abnormal rennin inhibitor values, whereas 16, or 80%, of the 20 major deviates had values outside this range.

§ West, P. M.: Personal communication to the authors.

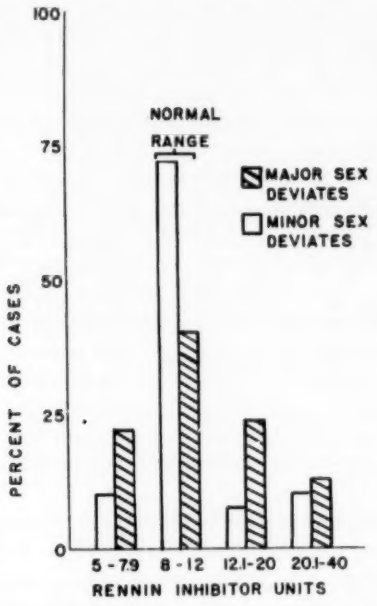

Fig. 2.—Comparison of minor and major sex deviates in terms of average concentration of rennin inhibitor present in blood serum.

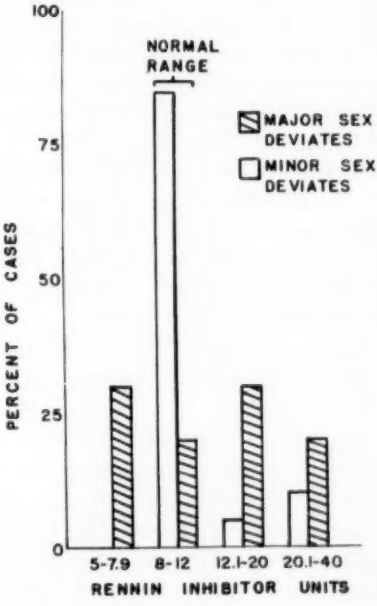

Fig. 3.—Comparison of sex offenders rated as extremes along a dimension of "degree of sexual deviation" in terms of average rennin inhibitor values present in blood serum.

These results suggest that psychiatrically determined major and minor deviant groups among hospitalized sex offenders can be distinguished at a statistically significant level on the basis of this biochemical measure. In the population studied, major and minor groups differed not only in terms of reactivity to a stress situation but also in their average rennin inhibitor levels, with values for the major deviants tending toward the extremes.

COMMENT

Other investigators || have suggested that high rennin inhibitor levels are characteristic of immaturity and growth and are correlated [4] in schizophrenics with the adoption of immature regressive defenses under prolonged stress. Results reported in this paper suggest a somewhat different formulation for nonpsychotic sex offenders, since not only elevated but depressed and variable rennin inhibitor values found in major deviates tend to be associated with immaturity. From inspection of the case histories and probation reports of the subject group, it appears that major sex offenders are less mature emotionally and have lower frustration tolerance, and perhaps, less adequate ego defenses, than minor offenders. This is evidenced in their greater tendency to act out sexual and aggressive impulses without regard to the consequences.

The psychiatric ratings were presumably based on the degree of emotional illness as manifest in the sexual behavior of the offender. If the ratings were, in fact, made in accordance with this criterion, our results point to a relation between mean level and variability of rennin inhibitor and degree of emotional disturbance in those nonpsychotic subjects who tend to act out conflicts or impulses through sexual behavior.

At least two aspects of the design and procedure of this investigation make it necessary to view our results as tentative. Perhaps most important of these is the fact that the difference obtained in mean rennin inhibitor levels between minor and major groups was not predicted by the original hypothesis but, rather, became evident in later manipulation of the data. Differences thus obtained are, of course, subject to error in that they may be a function of the particular samples drawn for study. Consequently, our results require confirmation in further studies.

A second factor is the fallibility of the ratings which formed the criteria. Although good agreement was obtained between raters, we cannot be sure that the basis of the rating judgment was actually that specified. Judgment could conceivably have been made on the basis of other factors, such as number of previous offenses, presence or absence of aggression in offenses, etc.

Despite these objections, it is hoped that our results may serve to stimulate further research into possible relationships between personality and biochemical factors.

SUMMARY

One hundred hospitalized men who had been convicted of some sex offense were divided into minor and major sexual deviate groups on the basis of collective psychiatric judgment. Determinations of rennin inhibitor levels in the blood serum of these subjects were made under varying conditions of stress. Major and minor sexual deviate groups were found to differ in terms of (*a*) the degree of variability of

|| References 1 through 3.

rennin inhibitor levels determined under stress conditions, with major offenders more variable than minor offenders, and (*b*) the average level of rennin inhibitor values, with major offenders tending to fall outside normal limits.

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EFFECT OF ATROPINE ON LEUCOCYTE COUNTS OF PATIENTS WITH MENTAL AND EMOTIONAL DISEASE

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SCHIZOPHRENIC subjects respond to the injection of 3 mg. of atropine sulfate by a slight decrease in systolic blood pressure. Those who are not schizophrenic respond with an increase.[1] It was suggested [1] that in the latter group the atropine stimulated the sympathetic ganglia to release epinephrine. Schizophrenics, with an underreactive sympathetic system, are not able to do so.

When epinephrine is injected, it produces a marked leucocytosis in two phases. In the first phase there is a maximum, 17 minutes after injection, of neutrophiles, lymphocytes, and eosinophiles. In the second phase the neutrophiles continue to rise but the lymphocytes and eosinophiles decrease.[2] Since schizophrenics react normally to injected epinephrine,[3] the leucocyte response to atropine may give indirect evidence for or against the suggestion that schizophrenics are not able to release epinephrine. If the hypothesis is correct, atropine should produce an increase in neutrophiles and a decrease in lymphocytes and eosinophiles in nonschizophrenic, but not in schizophrenic, subjects.

METHOD

Patients at the Munroe Wing of the Regina General Hospital were given routine atropine tests [1] within a few days after admission. All tests were started at 9:00 a. m. and atropine was given at 9:30 a. m. Samples of capillary blood were taken from the patients at 9:00 a. m. (before atropine) and at intervals after injection of atropine. The laboratory examinations were performed by the staff of the Regina General Hospital, who had no direct contact with, and were unaware of, the diagnosis of the subjects or of the results of the atropine test. Eosinophile counts were made using the Randolph technique. Each reported value is the mean of two pipettes. Other analyses included (1) total white blood cell count; (2) differential count for neutrophiles, lymphocytes, and monocytes; (3) hemoglobin; (4) hematocrit; (5) erythrocyte sedimentation rate, and (6) blood sugar.

Patients were sorted into two diagnostic groups,[2] schizophrenics and others, diagnoses in the latter group including neuroses, depressions, and psychopathic states. All diagnoses were established by the clinical staff of the Munroe Wing, who were not informed of the laboratory results.

RESULTS

Values for hemoglobin, hematocrit, blood sugar, and erythrocyte sedimentation rates are shown in Table 1. Within two hours after injection there is no drift in any of these variables for either diagnostic group. Differences between the groups are small. Atropine has no effect on hemoconcentration.

Director of Psychiatric Research, Psychiatric Services Branch, Department of Public Health.
Saskatchewan Committee on Schizophrenic Research; supported by the Department of National Health and Welfare, Canada.

The effect of atropine on leucocyte values up to four hours after injection is shown in Table 2. Atropine produces the following changes in leucocytes: 1. No drift in neutrophiles, either up or down, at the four-hour level in schizophrenics, but a decrease after one hour and recovery by four hours. The mean value four hours after atropine injection is below the preatropine value. Other diagnostic groups show a marked increase in neutrophiles with time, and the four-hour mean is higher

TABLE 1.—*Changes in Blood Values of Schizophrenics and Other Diagnostic Groups After Injection with 3 Mg. of Atropine Sulfate*

Variable	Time, A. M. 9:00	10:30	11:00	11:30
Schizophrenics (Eight Patients)				
Hemoglobin, mg./100 ml.	15.3	15.4	15.2	15.4
Hematocrit, ml./100 ml.	46.8	46.4	45.8	45.3
E. S. R., mm./60 min.	5.9	7.1	5.4	6.6
Sugar, mg./100 ml.	105	102	102	102
Other Diagnostic Groups				
Hemoglobin	13.9	13.8	13.7	13.7
Hematocrit	44.8	43.6	43.8	44.2
E. S. R.	16.0	17.0	13.3	15.5
Sugar	107	105	101	100

TABLE 2.—*Change in Leucocyte Count in Schizophrenic and Other Diagnostic Subjects After Injection with 3 Mg. of Atropine Sulfate*

Variable	Time 9:00 a.m. Preatropine	10:30 a.m.	11:30 a.m.	12:30 p.m.	1:30 p.m.	Mean Atropine Values
		Atropine				
Schizophrenic						
No. patients	37	28	37	18	18	.....
Total leucocytes	7,879	7,321	7,497	7,374	7,953	7,536
Neutrophiles	5,053	4,754	5,080	4,774	5,142	4,938
Monocytes	357	283	347	269	273	293
Lymphocytes	2,192	1,991	1,838	2,076	2,261	2,042
Eosinophiles	153	138	133	169	182	156
Other Diagnostic Groups						
No. patients	38	23	38	14	14	.....
Total leucocytes	7,361	7,516	7,278	8,123	8,654	7,893
Neutrophiles	4,508	4,820	4,914	5,199	5,623	5,139
Monocytes	381	323	331	412	441	377
Lymphocytes	2,178	2,016	1,751	1,992	2,245	2,001
Eosinophiles	134	92	101	86	92	93

than the preatropine value. 2. A decrease in lymphocytes two hours after injection, more pronounced in other diagnostic groups, with a return to normal levels by 1:30 p. m. 3. A decrease in monocytes one hour after atropine, followed by restoration to pretreatment values for the other groups. 4. A decrease in eosinophiles at one hour, sustained for four hours with other diagnostic groups, in contrast to a very slight decrease in schizophrenics at the two-hour level and an eventual rise, so that the mean atropine value is greater than the preatropine value.

Changes in leucocyte values two hours after injection are shown in Table 3.

Samples of blood were taken from a smaller group of patients the day before the atropine test. The results are given in Table 4. There was no interruption in the morning routine for these patients. These values, a sample of the diurnal rhythm, are compared with results for the same time interval after atropine injection.

From 9:00 a. m. to 1:30 p. m. there was an increase in the neutrophiles, more pronounced in the nonschizophrenic group, a decrease in monocytes, no change in lymphocytes, and a decrease in eosinophiles in schizophrenics but not in the other group. Atropine decreased neutrophiles in schizophrenics but did not change monocyte, lymphocyte, or eosinophile values. In the other groups atropine did not change the trend of movement in neutrophiles and monocytes, but lowered the lymphocyte and eosinophile values.

TABLE 3.—*Change in Leucocyte Values Two Hours After Injection of Atropine*

	Percent Change	
	Schizophrenia	Other Diagnoses
Total count	— 5	0
Neutrophiles	0	+ 9
Monocytes	0	—13
Lymphocytes	—16	—20
Eosinophiles	—13	—25

TABLE 4.—*Four-Hour Change in Leucocyte Counts With and Without Atropine Injections*

	Schizophrenia				Other Diagnoses			
	No Atropine		With Atropine		No Atropine		With Atropine	
Variable	9:00 a.m.	1:30 p.m.	9:00 a.m.	1:30 p.m.	9:00 a.m.	1:30 p.m.	9:00 a.m.	1:30 p.m.
No. patients	13	13	13	13	10	10	10	10
Total count	8,473	8,512	8,035	7,612	7,770	8,500	8,929	9,013
Neutrophiles	5,400	5,629	5,084	4,717	5,167	5,886	5,569	6,137
Monocytes	305	216	328	291	347	270	369	278
Lymphocytes	2,364	2,324	2,311	2,310	2,056	2,047	2,372	2,064
Eosinophiles	260	151	207	207	104	100	123	96

COMMENT

The changes in leucocytes must be measured against the base line of the diurnal rhythm present in the subject. It has been shown * that there is a regular morning decrease in the eosinophile count after arising. The greatest decrease occurs at 9:30 a. m., and after that the eosinophiles begin to rise. The decrease is related to time of awakening. Between 9:30 a. m. and 1:30 p. m. there is a rise in eosinophiles.

The eosinophile change in the other nonschizophrenic group reported here fits in with this usual diurnal rhythm. However, the schizophrenics show a decrease in eosinophiles between 9:30 a. m. and 1:30 p. m., which is contrary to the normal shift upward for normals. If it is assumed that the diurnal drop of schizophrenics occurs several hours later in the morning, then this finding becomes consistent. One needs to assume that in schizophrenics the major decrease in eosinophiles occurs between 10:00 a. m. and 2:00 p. m. rather than, as with normals, between 7:00

* References 4 and 5.

a. m. and 9 : 30 a. m. In other words, the diurnal drop is of normal intensity but is shifted along the time axis. Atropine, in the other group, produces a further decrease in the eosinophile count and in schizophrenics prevents the diurnal drop from occurring.

There is a diurnal rise in the neutrophiles in both groups, which is reversed by atropine in the schizophrenic group. No change in the lymphocytic diurnal rhythm is produced by atropine in schizophrenics, but there is a decrease in the other group.

In other diagnostic groups atropine accentuates the normal diurnal rhythm, whereas in schizophrenics it inhibits the normal diurnal rhythm. In all tests of schizophrenic reactivity one will have to know the normal diurnal rhythm which is the base line for comparison. It is possible that in order to obtain comparative tests of eosinophile response to any agent, one should start the test after the lowest point of the diurnal rhythm has been reached. Thus, if the lowest point is reached in schizophrenics at 2 : 00 p. m., one should begin the test then, rather than start all tests at 8 : 00 or 9 : 00 a. m. If it is true that the diurnal rhythm varies in time between these groups, then comparative single values for eosinophiles are valueless, since schizophrenics will have higher or lower eosinophile values depending upon the time selected for sampling. A complete investigation must report the entire diurnal change for a large group.

The hypothesis that atropine releases epinephrine in other diagnostic groups is further reinforced. This does not occur in schizophrenics.

CONCLUSIONS

Atropine produces in neuroses and depressions and in psychopaths, an increase in neutrophiles and a decrease in monocytes, lymphocytes, and eosinophiles. In schizophrenics these changes do not occur. Atropine accentuates the normal diurnal rhythm of these other diagnostic groups and inhibits the rhythm for schizophrenics.

Dr. B. Gaerber, Clinical Director, Munroe Wing, permitted the performance of tests on Wing patients; J. Stephen, Director of Laboratories, Regina General Hospital, cooperated in the research project; A. Trew made chemical analyses, and M. Nix performed hematological analyses.

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INFLUENCE OF E. C. T. AND INSULIN COMA ON LEVEL OF ADRENOCORTICAL STEROIDS IN PERIPHERAL CIRCULATION

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THE VALUE of insulin coma and electroshock in the treatment of certain schizophrenic conditions and major affective disorders is well established. Despite the wide application of these procedures, the exact mechanisms of action responsible for therapeutic success are obscure.[1] The recent interest and important advances in the field of adrenocortical physiology, combined with the conceptualization of a "general stress" theory,[2] have influenced many investigators to study the effect of these "shock" procedures upon adrenocortical activity.*

All previous reports have been based upon changes in nonsteroid constituents of the plasma, alterations in the number of circulating lymphocytes and eosinophiles, or variations in the end-products of steroid metabolism found in the urine.* As all of these measurements are indirect and often unreliable indications of adrenocortical activity, it seemed important to reexamine this problem, using the technique of Nelson and Samuels for 17-hydroxycorticosteroids (17,21-dihydroxy-20-ketosteroids) in blood.[24] Since 17-hydroxycorticosterone (Compound F) appears to be the principal adrenal steroid in the peripheral and adrenal venous blood of man † which has this structure, this technique permits a more direct and precise appraisal of concentrations of adrenal metabolic hormones.

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This investigation was supported in part by a research grant M-451 from the National Institute of Mental Health, of the National Institutes of Health, United States Public Health Service, and in part by the Scottish Rite Foundation.

Carma Darley, Beth Dowding, Dean Baskin, and Rosalind Walton gave technical assistance. Dr. Owen Heninger and Dr. Eugene Wiemers, of the Utah State Hospital, and their staff, in particular, Josephine Whightman and Mary Startup, cooperated and aided in the study.

* References 3 through 23.

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METHOD

Subjects were patients on the psychiatric wards of the Salt Lake County General Hospital and the Utah State Hospital. All were ill with acute schizophrenic psychoses. These were either initial psychotic episodes or acute recurrences following a period of remission. In several cases manic or depressive features were prominent. The only exceptions were four deteriorated subjects with chronic hebephrenic schizophrenia who had been hospitalized five years or more at the Utah State Hospital for their illness. Twenty-five subjects, 7 male and 18 female, were studied with electroshock therapy. Eight subjects, four male and four female, were studied during insulin coma therapy.

All patients who received electroshock therapy, except for the four with hebephrenic schizophrenia, were premedicated with 1.2 mg. of atropine. Twenty-six studies were made with the Lektra Laboratories, Inc., machine, Model 160G, using alternating current, which was increased over a 1.2-second period to 160 volts (glissando E. S. T. time). In the present report this procedure has been designated as the "glissando technique." Five subjects were studied with the Reiter Electrostimulator, Model CW47B, which utilizes a unidirectional pulsating current.[27]

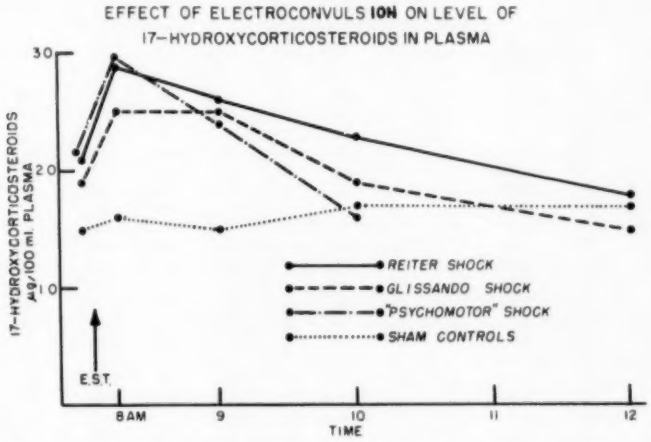

Fig. 1.—Effects of electroconvulsive seizures on the plasma levels of 17-hydroxycorticosteroids. The sham controls were treated in the same way as the other subjects, but no shock was administered. Normal untreated subjects show an average drop of 5 γ per 100 ml. of plasma over the four-hour period.

Nine were premedicated with diphenylhydantoin (Dilantin) or SKF 2599 (a diphenylhydantoin congener in which carbon-2 is completely reduced), agents used to modify seizures, and then received electroshock with the glissando technique. A standard procedure was followed. Thirty-milliliter blood samples were drawn at 8:00 a. m., prior to therapy, and at one-quarter, one, two, and four hours following the electroshock treatment.

In the case of the insulin coma studies blood samples were drawn at 6:30 a. m., preceding the administration of insulin, and at 8:00, 9:00, 10:00, and 11:30 a. m., after the administration of insulin.

Blood samples were placed in tubes containing 4 mg. of heparin. These were then centrifuged, the plasma removed, and the samples refrigerated until analyzed. The 17-hydroxycorticosteroids in the plasma were measured by the procedure of Nelson and Samuels.[24] Blood sugar was determined by Nelson's modification of Somogyi's method.[28] Eosinophile counts were performed in duplicate by the method of Randolph.[29] The white blood cell counts were determined by conventional techniques, and the absolute number of lymphocytes was calculated from this and a 200-cell differential count.

RESULTS

1. *Electroshock—Glissando Technique.*—The glissando technique was used to induce grand mal convulsions in 22 studies on nine subjects with acute schizophrenic psychoses. Control studies were done on six of these subjects, the same routine being followed with shock excluded.

Significant steroid rises occurred one-quarter or one hour after the convulsions in 18 experiments. In four studies statistically significant increases were not present. For the entire series there was a mean increase of 7 γ per 100 ml. of plasma at both one-quarter and one hour after the seizures. Both elevations were significant ($P < 0.01$) ‡ (Fig. 1; Table 1).

TABLE 1.—*Effect of Electroconvulsion (Glissando Technique) on Level of 17-Hydroxycorticosteroids, Eosinophiles, and Lymphocytes*

			17-Hydroxycorticosteroids, γ/100 Ml., Plasma					Eosinophiles, % Change		Lymphocytes, % Change	
Subject	Sex	Date	Control	¼ Hr.	1 Hr.	2 Hr.	4 Hr.	2 Hr.	4 Hr.	2 Hr.	4 Hr.
F	F	11/23	13	..	22	10	..	....	....	....	....
C	M	12/20	35	42	31	31	..	−87	....	−60	....
C	M	12/28	26	19	18	11	15	−28	−32	+17	0
C	M	1/14	16	18	12	14	12	−28	+20	....	−7
C	M	2/ 5	18	27	24	16	14	+30	−12	0	+42
J	F	12/21	18	30	23	21	18	....	....	+12	....
J	F	12/26	19	26	38	21	13	−62	−62	0	−15
J	F	1/ 9	16	26	24	17	16	−43	−29	−41	−12
E. M.	F	1/12	20	26	..	26	12	−86	−86	+25	−50
E. M.	F	1/16	21	19	23	15	14	−56	−48	−22	−44
E. M.	F	2/11	18	28	22	14	11	−46	−46	−44	−22
H. C.	M	1/18	23	27	30	24	24	−65	+35	0	+62
H. C.	M	1/21	22	23	18	18	10	−58	−27	−26	+20
H. C.	M	1/22	16	34	30	26	9	−42	+126	−14	−17
H. C.	M	2/ 4	15	18	19	16	..	−62	−55	−61	+3
D. S.	F	1/14	2	2	21	..	5	....	−53	−22	+51
D. S.	F	2/ 6	15	23	32	26	19	−67	−30	−6	+29
D. S.	F	2/13	11	22	20	17	7	−50	−72	−53	−29
M	F	5/ 9	22	34	39	38	22	−27	−19	....	+130
M	F	5/15	17	25	18	15	6	−17	−17	....	....
N	F	5/16	25	..	31	14	14	....	−71	....	....
H	F	6/ 2	15	29	30	20	11	−12	−50	....	−33
Average			19.1	26.1	25.2	19.0	13.7	−45	−28	−18	0

Six subjects were studied more than once. The same subject showed considerable variation in steroid responses on these different occasions. As examples, both Subjects C and H. C. developed no steroid increases following electroshock therapy on at least one test; yet on preceding and subsequent studies both demonstrated significant rises. In several cases maximum increases appeared early in the course of treatment; in others the greatest rises occurred late in therapy, after 10 or more electroshock treatments had been administered.

2. *Electroshock Therapy—Glissando Technique—Results with Hebephrenic Schizophrenics.*—Since three subjects on at least one occasion failed to show significant increases in the plasma 17-hydroxycorticosteroids despite the occurrence of typical electrically induced grand mal seizures, it was postulated that some relation-

‡ Determined on the basis of Fisher's table of *t*.

ship might exist between the occasional lack of adrenocortical reactivity and the possibility of an ultimately unfavorable therapeutic course. Four hebephrenic schizophrenics were therefore studied. All had been psychotic for five years or more, and each was an extremely regressed patient on a chronic ward of the Utah State Hospital. In every case significant increases in the level of 17-hydroxycorticosteroids appeared after electroshock ($P < 0.01$). The mean increases were of the same order as in the first series (Table 2). It was concluded that a low adrenal steroid response to electroshock was not characteristic of chronic deteriorated schizophrenics and could not, therefore, be considered as prognostic of such development without a study of the subsequent course of patients originally known to have an occasional reduced response.

TABLE 2.—*Effect of Electroconvulsion (Glissando Technique) on Level of Plasma 17-Hydroxycorticosteroids in Chronic Hebephrenic Schizophrenics*

		17-Hydroxycorticosteroids, γ/100 Ml. of Plasma				
Subject	Sex	Control	¼ Hr.	1 Hr.	2 Hr.	4 Hr.
H	M	18	20	28	33	24
V. B.	M	11	..	24	24	25
R	F	24	31	27	22	14
B	F	21	18	28	19	8

TABLE 3.—*Effect of Electroconvulsion (Reiter Machine) on Level of Plasma 17-Hydroxycorticosteroids*

		17-Hydroxycorticosteroids, γ/100 Ml. of Plasma				
Subject	Sex	Control	¼ Hr.	1 Hr.	2 Hr.	4 Hr.
T	M	14	35	32	24	14
T	M	28	20	24	25	22
W	F	16	24	20	21	..
A	M	22	35	28	20	..
Mc	F	23	31	24	24	19

3. *Electroshock Therapy—Reiter Machine.*—The mode of administration of electroshock was varied to determine whether this might influence the pattern of steroid response. The five subjects studied exhibited consistent steroid elevations following the induction of seizures by the Reiter machine. These increases were of the same magnitude and degree of significance ($P < 0.01$) as those obtained with the glissando technique (Fig. 1; Table 3). Since the form of current differed, it seemed probable that the steroid response was not a function of the particular technical procedure used to induce a seizure but was the result either of cerebral dysrhythmia and discharge or of the physiological changes associated with any grand mal convulsion.[30]

4. *Nonconvulsant Electroshock—Glissando Technique with Diphenylhydantoin Sodium or SKF 2599.*—Nonconvulsant electroshock was studied to determine whether the steroid increases following a grand mal seizure were a function of the apnea, cyanosis, and violent muscular activity or were the result of cerebral discharge. A group of subjects were premedicated with diphenylhydantoin sodium or SKF 2599 for several days and then subjected to electroshock, with use of the

glissando apparatus. In three of these subjects the diphenylhydantoin failed to modify the seizure, and a normal grand mal response occurred. In these cases steroid rises were present and were in the same range as those elicited with the glissando technique alone or with the Reiter apparatus (Table 4). Four subjects on diphenylhydantoin medication and two on SKF 2599 failed to convulse when shocked. Instead, they exhibited a psychomotor-like response, characterized by random movements of the head, arms, and legs, sucking, disorientation, and amnesia. There was no apnea, cyanosis, or significant muscular activity. Despite this, the levels were all

TABLE 4.—*Plasma 17-Hydroxycorticosteroid Responses*

Subject	Sex	17-Hydroxycorticosteroids, γ/100 Ml. of Plasma				
		Control	¼ Hr.	1 Hr.	2 Hr.	4 Hr.
"Psychomotor" Seizures—Premedication with Diphenylhydantoin Sodium or SKF No. 2599						
D	F	21	23	20	12	..
D	F	17	29	23	19	..
B	F	24	36	28	15	..
G	F	14	21	19	14	..
R*	F	31	39	33	23	..
B*	M	20	28	22	13	18
Grand Mal Seizures—Premedication with Diphenylhydantoin Sodium						
B. L.	F	20	26	27	17	
H	F	25	24	36	25	
H	F	21	30	30	38	

* Premedication with SKF No. 2599.

TABLE 5.—*Insulin Coma—Data*

Subject	Sex	Length of Therapy, No. of Coma Hr.	Insulin Dose Units	Period of Coma	17-Hydroxycorticosteroids, γ/100 Ml. of Plasma					Eosinophiles, % Change in 5 Hr.	Lymphocytes, % Change in 5 Hr.	Blood Glucose, Mg./100 Ml.	
					Control, 6:30 A. M.	8 A. M.	9 A. M.	10 A. M.	11:30 A. M.			Control	Lowest Level
S	M	8½	130	8:30-10:00	19	28	32	34	24	—93	—56	74	2
D	M	59	120	9:05-10:50	..	12	24	24	23	—80	—38	78	6
S	M	14	120	8:45-10:15	18	16	27	21	25	—81	....	72	2
W	M	57½	220	9:45-10:35	11	9	20	17	17	—73	—62	..	..
F	F	45	40	8:20-10:30	17	27	32	37	31	—74	—22	68	6
M	F	7	140	9:20-10:50	14	19	21	28	26	—31	—42	..	..
N	F	3½	250	8:50- 9:50 (Semicoma)	7	17	30	22	30	—90	—75	..	..
L	F	40	130	9:25-10:50	10	17	17	25	21	—71	—28	90	4

significantly elevated 15 minutes after the treatment ($P < 0.01$) but fell off more rapidly than those following the violent, complete grand mal seizures, a response suggesting that steroid elevations were in small part influenced by the respiratory arrest and muscular spasm but were more significantly related to the induced cerebral dysrhythmia and cortical discharge (Fig. 1, Table 4).

5. *Insulin Coma Therapy.*—The histories of eight subjects receiving treatment on the insulin wards of the Utah State Hospital were studied. The subjects were selected to include four who were in the early stages of treatment and four who had received 40 hours or more of coma therapy and were close to termination. These studies were made on a Thursday and had been preceded by three consecutive days of insulin coma treatment that week. As indicated in Table 5, every subject demon-

strated significant steroid increases under the stress of this procedure. Concomitant blood sugar and hematological studies were made. There was a consistent eosinopenia, lymphopenia, and leucocytosis five hours after the administration of insulin. During the period of insulin coma blood sugar values dropped to levels of

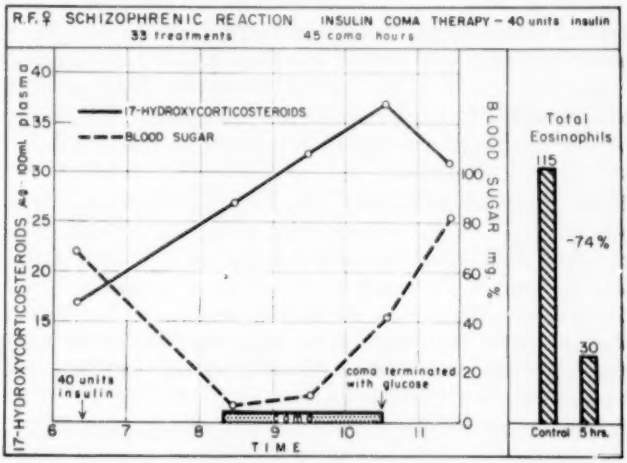

Fig. 2.—Changes in blood sugar, eosinophiles, and plasma 17-hydroxycorticosteroid levels in a schizophrenic patient given insulin coma therapy.

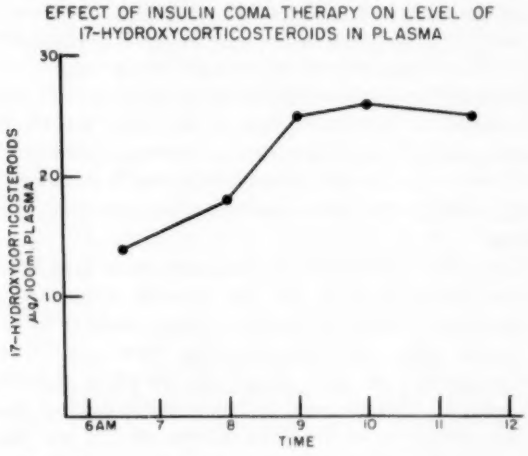

Fig. 3.—Effect of insulin coma therapy on the level of 17-hydroxycorticosteroids in plasma. Average curve for eight subjects. Normal persons show a mean decrease of 7 γ per 100 ml. of plasma over this period.

2 to 10 mg. per 100 cc. A typical example of the total effects in one patient is charted in Figure 2, and the mean steroid changes for the group are demonstrated in Figure 3.

Noteworthy was the absence of any obvious difference in the responses of those subjects who had just begun treatment and those who had been receiving insulin five times a week for several months. There did not appear to be any adaptive reaction or evidence of adrenal exhaustion.

COMMENT

All previous techniques that have been used to evaluate adrenocortical function in the human have been indirect and often unreliable. The virtue of the present procedure lies in its specificity for steroids having the side-chain characteristic of the metabolic hormones of the adrenal cortex. Consequently, the influence of electroshock or insulin coma can be measured in terms of its effect on the levels of these hormones in the peripheral blood.

Both insulin coma and electroshock caused significant elevations in blood steroids. Whether these changes in the concentration of adrenal steroids in the peripheral circulation represent an increase in adrenocortical activity is as yet unsettled. Until further data are available, it would be hazardous to assume a direct relationship between the changes in the levels of the steroids peripherally and the rate of elaboration of hormones from the gland. What does seem evident is that these shock therapies cause an increase in the concentration of circulating adrenal steroids to which the cells of the body are subject.

Since nonconvulsive electroshock therapy induces changes comparable to those with convulsant therapy, it seems probable that the increases after convulsions result, in the main, from cortical discharge and are determined only in part by carbon dioxide, electrolyte, and other chemical changes in the peripheral tissues which follow the violent grand mal reaction. One might speculate that these steroid changes are mediated by a direct action on the hypothalamic-pituitary system, but there are no adequate data, as yet, to document such a conclusion. It is interesting that the elevations of steroids after electroshock are comparable in degree to those following 0.1 to 1.0 I. U. of corticotropin administered intravenously.[31] Unexplained is the considerable variation in steroid response in the same subject from test to test, despite the fact that seizures in all cases, except those modified by diphenylhydantoin and SKF 2599, were of identical type and comparable duration. In at least four instances no significant steroid rises occurred in the presence of a fully developed grand mal seizure.

Although it has been postulated that schizophrenics have hyporeactive adrenal cortices,§ with the exception of the few tests already enumerated, all schizophrenic subjects demonstrated significant 17-hydroxycorticosteroid elevations following electroshock and insulin coma. In particular, four deteriorated hebephrenic subjects gave significant responses to E. S. T., despite the chronicity of their disease and their unfavorable prognosis. There seemed to be no clearly evident correlation between the prognosis and chronicity of the schizophrenic process and the capacity of the organism to respond to the stress of electroconvulsion with increases in the levels of 17-hydroxycorticosteroids in the peripheral circulation.

The responses to insulin coma therapy were uniform and of a considerable magnitude. As several of the subjects had been receiving insulin coma therapy five days a week for a number of months prior to this study and as this was the fourth consecu-

§ References 32 through 34.

tive coma treatment during that particular week, it seems probable that insulin coma will routinely produce steroid elevations. Apparently, such an acute stress, even though frequently repeated, causes little if any reduction in adrenal responsiveness.

Since adrenocortical steroids have been therapeutically effective in so many disease processes, it has seemed possible that the increase in adrenal steroids induced by both shock therapies might play an important therapeutic role in schizophrenia. In opposition to this point of view is the consistent rise in steroids in patients who failed to respond to insulin coma or electroshock with any therapeutic benefit. Furthermore, the changes following electroshock therapy are comparable to those found after the intravenous administration of small amounts of corticotropin. Much larger quantities of corticotropin have been given experimentally to schizophrenic subjects and have failed to produce any consistent therapeutic success.|| It would seem, therefore, that the increase in adrenocortical steroids which occurs after these procedures is a coincidental change and does not account for the therapeutic effectiveness of either technique.

CONCLUSIONS

1. Electroconvulsions induced either by alternating current (glissando technique) or unidirectional current (Reiter Electrostimulator) produced in most cases significant elevations in the levels of the 17-hydroxycorticosteroids of the blood. The type of current used to elicit a grand mal seizure did not appear to influence the degree of steroid change. The increases observed were equivalent to those found after a single intravenous injection of 0.1 to 1.0 I. U. of corticotropin.

2. Grand mal seizures were blocked by premedication with diphenylhydantoin (Dilantin) sodium and SKF 2599 to eliminate the apnea, cyanosis, and violent muscular movements of a full-blown convulsion. Psychomotor-like seizures resulted and were associated with steroid rises as great as, but somewhat shorter in duration than, those observed with unmodified electroconvulsions, these findings suggesting that the major factors responsible for steroid elevations following electroshock were the cortical dysrhythmia and the central nervous system discharge.

3. Significant increases in the concentration of the 17-hydroxycorticosteroids in the blood occurred on every occasion with insulin coma.

4. The increases in the plasma 17-hydroxycorticosteroids as a result of both types of shock therapy do not appear to be therapeutically significant and do not explain the effectiveness of these procedures.

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RIBOSURIA IN MUSCULAR DYSTROPHY

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MINOT, Frank, and Dziewiatkowski [1] in 1949 reported on the discovery of pentose- and phosphorus-containing complexes in the urine of patients with progressive muscular dystrophy. They found that when 8 to 10 drops of urine from a patient with a disorder of this type was heated in a boiling water bath for 45 minutes with 5 cc. of Benedict's qualitative solution, reduction was invariably obtained. The substance responsible for this reduction was identified as *d*-ribose, which is excreted as a phosphorus-containing complex. Orr and Minot [2] suggested that this observation could be made the basis of a diagnostic test for muscular dystrophy. They examined specimens of urine from 26 cases of progressive muscular dystrophy of all types, from 6 of dystrophia myotonica, from 5 of myotonia congenita, and from 3 of amyotonia congenita and discovered ribose in all of them. On the other hand, a negative result was obtained when testing urine from patients with a wide variety of neurological disorders, including muscular atrophy and disseminated sclerosis. They suggested that the presence of ribose was due to a specific error of cell metabolism occurring in muscular dystrophy but not in cases of neuropathic muscular atrophy.

Matthews and Smith,[3] in attempting to confirm these results, utilized a sensitive paper chromatographic technique for the detection of ribose and examined 24-hour specimens of urine from six cases of muscular dystrophy, two of dystrophia myotonica, one of ocular myopathy, and two of acute anterior poliomyelitis. They found no evidence of excretion of significant amounts of ribose in any of their cases and concluded that a test based upon the detection of ribosuria was of no value in differential diagnosis.

Drew and Selving,[4] on the other hand, confirmed the demonstration of pentosuria in cases of muscular dystrophy. In common with the experience of Orr and Minot, they failed to demonstrate this substance in the urine from cases of spinal muscular atrophy. However, they did obtain positive results in patients suffering from many different neurological diseases, including multiple sclerosis, cerebral palsy, and convulsive disorder. Furthermore, they were able to produce osazone crystals

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indistinguishable from those of *d*-ribose in certain cases of muscular disease which had yielded negative results when the test procedure described by Orr and Minot [2] was performed.

In this paper we report the results obtained by applying the technique described by Orr and Minot [2] to the examination of specimens of urine from 94 patients, of whom the majority were suffering from some form of myopathy.

MATERIAL AND METHODS

Twenty-four hour specimens of urine were obtained from a total of 89 cases of myopathy—46 of the Duchenne type of muscular dystrophy, 14 of facioscapulohumeral muscular dystrophy, 16 of limb-girdle type, and 13 of dystrophia myotonica. The method of classification in these cases is described in detail elsewhere.[5] Similar specimens from two patients with motor neurone disease and from three other patients with neuropathic muscular atrophy were examined; when the investigation was first projected, it was proposed to examine specimens from numerous control subjects and from other patients with neuropathic disorders, but the results obtained from a number of early cases made this project unnecessary. None of the patients had received any fruit during the 24 hours previous to the time at which the specimens were obtained.

Results of Testing for Ribosuria in Ninety-Four Cases

Diagnosis	No. of Cases	Ribosuria Found
Duchenne type muscular dystrophy	46	10
Facioscapulohumeral muscular dystrophy	14	0
Limb-girdle dystrophy	16	1
Dystrophia myotonica	13	1
Progressive muscular atrophy (motor neurone disease)	2	2
Polyneuritis	1	0
Peripheral nerve injury	1	0
Cervical spondylosis	1	0
Total	94	14

The specimens were examined for the presence of ribose by the technique described by Orr and Minot.[2] The observer performing the test was not aware as to whether the urine being examined was from a case of myopathy or from a patient with some other disorder.

RESULTS

The results obtained from our cases are given in the accompanying Table.

It will be noted that in our cases ribosuria was found in only a small number of myopathies, but it was also discovered in two cases of motor neurone disease. Though commoner in the Duchenne type cases, in which the disease process is more rapidly progressive than in the other forms of myopathy, there was no clear evidence that it was commoner in advanced cases, as the test was negative in some of our most severely disabled patients.

COMMENT

Our observations, though confirming the finding that ribose is excreted by a small proportion of patients with myopathy, have also revealed that similar findings may be obtained in patients with neuropathic muscular atrophy. If, as Orr and Minot [2] suggested, ribosuria is confined to the myopathies, it is difficult to understand the positive results they obtained in cases of "amyotonia congenita"; it is recognized that most patients to whom this diagnosis is applied turn out to be suffering from progressive infantile muscular atrophy,[6] a myelopathic disorder, and cases of the myopathic form of amyotonia appear to be of extreme rarity.[7]

We must conclude that ribosuria, while occurring in a small proportion of cases of myopathy, may also be found in patients with neuropathic muscular atrophy. Hence, as Matthews and Smith [3] have said, a test based upon this finding is of no value in the differentiation between myopathy and other conditions producing muscular atrophy. We would agree with Drew and Selving [4] that considerable caution should be exercised in the interpretation of ribosuria until more basic biochemical data are available.

SUMMARY AND CONCLUSIONS

A test for ribosuria, as described by Orr and Minot, was carried out on specimens of urine from 89 cases of myopathy and gave a positive result in 12 (13.5%); ribosuria was also discovered in samples from 2 cases of motor neurone disease.

It is concluded that a test for the detection of ribosuria is of no value in the diagnosis of myopathy.

Prof. F. J. Nattrass permitted the publication of these results, and Mr. R. J. Merrills gave technical assistance.

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STATISTICAL CONTROL STUDIES IN NEUROLOGY

V. The Rossolimo Sign

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IN VIEW of the divergent opinions expressed as to both the frequency and the value of the Rossolimo sign, we studied several control groups to determine the incidence and possible significance of this sign.

Markow [1] examined 700 clinically well people; no typical Rossolimo sign was found; in 4 the Babinski and in 5 the Oppenheim sign was elicited. Szebesta * found the Rossolimo sign in 13 of 400 aviation candidates; 2 of them had syphilis, and 4 probably had multiple sclerosis. Goldflam [2] found the sign absent in "thousands of people"; those that had a positive sign had latent diseases, especially multiple sclerosis. Weingrow [3] examined 76 patients without involvement of the central nervous system and stated that the Rossolimo sign can be found in normal persons with hyperactive reflexes. Finkelstein and Kaczyński [4] examined 1,000 patients in the surgical, medical, and gynecologic wards. The Rossolimo sign was observed in about 5% as the single pathologic sign of a neural lesion. A weak sign was found in 3%, a moderately strong one in 2%, and a very strong one in 0.6%, of the patients. The authors indicated that the sign may appear in the course of toxic conditions of the central nervous system which accompany general infectious diseases. Rimbaud, Serre, and Passouant [5] stated that, with the exception of 3 in over 5,000 cases, the Rossolimo sign indicated a pyramidal tract lesion. Rittmeister [6] examined 109 students between the ages of 16 and 19; only 2 had Rossolimo signs—1 had a spina bifida occulta and the other incipient multiple sclerosis. Carrara [7] elicited the Rossolimo sign in 30% of 50 normal cases.

The Rossolimo sign has been noted in association with various conditions; such as typhoid,[2] scarlet fever,[2] tetanus,† and uremia.[2] Rossen, Kabat, and Anderson [10] induced cerebral anoxia experimentally by arrest of the cerebral circulation in 10 cases of schizophrenia; the Rossolimo sign was demonstrated in 6 of the 10 cases. It disappeared a few seconds after release of the cuff. Kennard and Fulton [11] elicited

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* Szebesta: cited by Goldflam,[2] p. 50.

† References 8 and 9.

the Rossolimo sign after removal of Area 6 both in the chimpanzee and in man. The Rossolimo sign persists longer than the Babinski sign after anesthesia.[12]

Alterations of position, such as changing from the supine to the prone [2] or turning of the head to the side [6] do not result in disappearance of the Rossolimo sign. An Esmarch bandage has no effect on this sign.[6] The application of heat can bring out the sign. Warming the feet for 5 to 10 minutes at 40 C. (104 F.) brought it out in 7 of 50 subjects who did not have the sign previously.[6] We demonstrated the presence of the sign in two patients with multiple sclerosis after warming the feet for 10 minutes. Goldflam [2] stated that the Rossolimo sign does not disappear when the foot is put into cold water. However, in a series conducted by us it disappeared in three cases after immersion of the foot at 49 F., the time varying from 15 to 25 minutes; it diminished in two cases and remained in three cases. Savitsky and Karliner [13] noted the disappearance of the Rossolimo sign in a patient for two minutes after each electroshock treatment. We tested patients for exhaustion of the Rossolimo sign. After 200 tappings done on each of 12 separate occasions, at intervals of 72 hours, in 11 patients, it could still be obtained. Müller-Neff [14] also found it to be inexhaustible.

Goldflam [2] demonstrated the Rossolimo sign in infants up to one year of age. Rimbaud, Anselme-Martin, and Partelidés [12] found it to disappear at the age of 3 months; Rittmeister [6] found it absent at 1½ years of age, and Prissmann,[15] at 2 years.

One group of investigators states that the Rossolimo sign is a sign of organic involvement of the central nervous system—of the pyramidal tract.‡ Markow [1] illustrates the Russian view that it is a manifestation of the grasping tendency released by a lesion of the pyramidal tract. Goldflam [2] indicates that it is a sign of organic nervous disease and is due to involvement of an extrapyramidal tract, starting in the frontal cortex and continuing in the lateral column. Another group of investigators favor the view that the Rossolimo sign is not due to organic involvement of the nervous system.§ Krabbe and Ellermann [9] state that in diseases without pyramidal tract involvement, such as neurasthenia, polyneuritis, tabes dorsalis, and myositis, the Rossolimo sign was not observed. It was present in one case of depression, but the patient also had a doubtful Babinski sign. These authors concluded that this sign is not pathognomonic for any special disease; it is probably a pathologic increase of a normal latent reflex. Physiologically, the latent period of this reflex has been stated to be that of the so-called tendon, bone, or periosteal reflex and is much shorter than that of the skin reflex.[35] Wartenberg [36] concluded "that the Rossolimo reflex, valuable pyramidal sign as it is, is not in itself a pathologic reflex, but represents only a pathologic increase of a normally latent reflex."

Although the Rossolimo sign is often associated with increased muscle tone, it may be present even though there is a hypotonia.[8] It was still obtained in a case of subacute combined degeneration of the cord despite the change of the spastic paraplegia to a flaccid one. That hypertonia per se is not sufficient to produce the Rossolimo sign was demonstrated by Kino [37] in 1,000 examinations of 200 patients

‡ References 12 and 16 through 26.

§ References 27 through 34.

TABLE 1.—*Incidence of Rossolimo Sign in 2,500 Cases With Other Neurologic Findings*

Age, Yr.	Sex	Race	Unilateral	Bilateral	Diagnosis	Other Neurologic Findings
18	F	W	..	+	Incomplete abortion	Rt. abdominals not elicited
17	F	N	L	..	Pelvic abscess	Deep reflexes not obtained in lower ext.
26	M	W	R	..	Bronchiectasis	Rt. Gordon
27	F	W	R	..	Hematoma of vaginal wall	Rt. abdominals not elicited
40	M	W	..	+	Cervical myositis	Abdominals barely obtained, easily exhausted
31	M	W	..	+	Chronic cholecystitis	Weakness lt. lower; hyperreflexia; history of paresthesiae; lt. abdominals not elicited
32	F	N	..	+	Influenza	Abdominals not obtained; history of syphilis with treatment
49	M	W	L	..	Acute gastroenteritis	Urinary frequency; hyperreflexia; vibration diminished in rt. lower
28	M	N	..	+	Unresolved pneumonia	Position sense impaired in lowers; vibration diminished in rt. lower
50	F	W	L	..	Bronchitis	Bilateral Babinski; rt. Oppenheim sign; hyperreflexia; position sense diminished in lowers; Parkinsonism appearance; cogwheel movements of eyes
29	M	W	L	..	Gastroenteritis	Hyperreflexia; position sense diminished in lt. lower; nystagmus; history of paresthesiae, and visual difficulties
63	M	W	R	..	Arteriosclerotic heart disease	Rt. Oppenheim; pupils unequal; sluggish to light
60	F	W	L	..	Arteriosclerotic heart disease	Position and vibration sense diminished in lowers
40	F	W	R	..	Vaginal fistula	Abdominals not elicited
43	F	W	..	+	Fibromyomata of uterus	Ataxia in uppers; hyperactive reflexes
53	F	W	..	+	Hypertensive heart disease	Position sense impaired in toes
45	M	W	..	+	Coronary thrombosis	Nystagmus; impaired position sense in toes
23	F	W	..	+	Breast abscess	Nystagmus; ataxia; pallor of disc
24	F	W	..	+	Threatened abortion	Ataxia; nystagmus; position sense impaired in lt. lower; hyperreflexia
24	F	W	L	..	Influenza	Generalized hyperreflexia; abdominals barely obtained
46	F	N	L	..	Fibromyomata of uterus	Nystagmus; hyperreflexia; abdominals not elicited
73	M	W	..	+	Gastrointestinal malignant tumor	Lt. Hoffmann
42	F	W	L	..	Rheumatic heart disease	Hyperreflexia; bilateral Chaddock
25	M	W	..	+	Infectious mononucleosis	Nystagmus; hyperreflexia; position and vibration senses diminished in lowers; history of urinary frequency
39	M	W	..	+	Infectious arthritis	Bilateral Babinski; lt. central facial
42	F	W	..	+	Pneumonia	Deep reflexes all hypoactive
56	F	W	L	..	Hypertensive heart disease	Bilateral Hoffmann
64	M	W	L	..	Bronchopneumonia	Absent abdominals; vibration diminished in lowers; history of spinal anesthesia

treated by electroshock. In spite of the spacticity of the legs and strong ankle clonus, no Rossolimo sign could be demonstrated. The Rossolimo sign may persist for many years; Müller-Neff [14] found it still present 17 years after the onset of hemiplegia.

That the Rossolimo sign can be produced by a frontal lobe lesion without the presence of a Babinski sign was shown in the case with autopsy reported by Bartstra.[38] We had a similar case with a right hemiparesis, right Rossolimo sign, and bilateral

TABLE 2.—*Incidence of Rossolimo Sign in 2,500 Cases Without Other Neurologic Findings*

Age, Yr.	Sex	Race	Unilateral	Bilateral	Diagnosis
18	F	N	..	+	Gonorrheal arthritis
32	M	W	..	+	Infectious arthritis
24	F	W	..	+	Chronic cholecystitis
70	M	W	R	..	Emphysema; diabetes mellitus
23	F	W	R	..	Incomplete abortion
30	F	N	..	+	Retroverted uterus
13	F	N	L	..	Pulmonary tuberculosis
64	M	W	L	..	Arteriosclerotic heart disease
26	M	W	R	..	Rheumatic heart disease
44	F	W	L	..	Threatened abortion
63	F	W	R	..	Thyrotoxicosis
20	F	W	R	..	Pyelitis
64	F	W	R	..	Pelvic abscess
13	M	W	R	..	Rheumatic heart disease; chorea
45	M	W	..	+	Upper respiratory infection
51	M	W	R	..	Arteriosclerotic heart disease; history of head injury with skull fracture
37	F	W	R	..	Fibromyomata of uterus
36	M	W	R	..	Duodenal ulcer
32	M	N	R	..	Tuberculous pleurisy
15	F	N	..	+	Acute gonorrheal salpingitis
27	F	W	..	+	Missed abortion
34	F	W	..	+	Incomplete abortion
35	F	W	R	..	Rheumatic heart disease
58	M	W	R	..	Rheumatic heart disease
27	M	W	..	+	Catarrhal jaundice
34	F	W	L	..	Rheumatic heart disease
57	F	W	..	+	Hemorrhoids; history of head injury 4 yr. before
27	F	W	L	..	Pneumonia
28	M	W	L	..	Rheumatic heart disease; history of head injury at 8 yr. of age
58	M	W	..	+	Essential hypertension
45	M	W	..	+	Coronary thrombosis
33	M	W	..	+	Influenza
20	F	W	..	+	Uterine bleeding
36	F	W	..	+	Bronchial asthma
33	F	W	L	..	Chronic cholecystitis

papilledema. Air studies showed a space-occupying lesion of the frontal region on the left side. Unfortunately, operation and autopsy were refused.

That involvement of the brain is not essential to the Rossolimo sign is illustrated by the case of Petit-Dutaillis and Chavany [39] in a patient with progressive paraparesis, cerebellospastic gait, hyperreflexia in the lower limbs, bilateral Rossolimo signs, and diminution bilaterally to pain, temperature, and touch in the forearm, palm, and third, fourth, and fifth fingers. A disk was removed from the sixth intervertebral cervical space. A Babinski sign developed postoperatively. We also had a patient with weakness and spasticity in the lower limbs and a right Rossolimo sign. A cervical disk was removed; four months later the Rossolimo sign was not present.

MATERIALS AND METHODS

Five groups of patients were studied.

1. Patients with non-neurologic disease admitted to the surgical, medical, and obstetrical wards of the Morrisania City Hospital, 2,500. The age incidence of the group when graphed showed a bell-shaped curve, indicating that the sample was statistically valid. There were 1,695 females and 805 males. This ratio is greater than the ratio of 100.6 females to 100 males in the Bronx, according to the Census of 1930. The greater number of females is due probably to the large gynecologic division in this hospital. Negroes comprise 1.02% of the population of the county; of the series of 2,500 hospital patients, Negroes constituted 11.6% of those examined. The greater number of Negroes in the series is most likely due to economic conditions and the fact that the hospital is a city institution.

2. Inductees, 706—all male, between ages of 21 and 35.

3. Psychoneurotic patients, 444.

4. Patients with multiple sclerosis, 354.

5. Patients who had had head injuries, 2,612. The majority were cases of cerebral concussion with the postconcussion syndrome. The minority was constituted of cerebral lacerations, con-

TABLE 3.—*Résumé of Tables 1 and 2*

	Total No. of Cases	Bilateral Rossolimo Sign	Unilateral Rossolimo Sign	
			Right	Left
With other neurologic findings	28	14	4	10
Without other neurologic findings	35	15	13	7

TABLE 4.—*Incidence of the Rossolimo Sign with Age*

Age Group	0-19 Yr.	20-39 Yr.	40-59 Yr.	60 Yr. and Over
Total no. in this group	455	1,015	705	325
No. with Rossolimo sign	6	31	18	8
Incidence of Rossolimo sign, %	1.3	3.0	2.6	2.5

tusions, fractures of the skull, and subdural hematomas. The interval from the time of head injury to the time of examination varied from 4 weeks to 19 years.

Although Rossolimo elicited the sign by flicking the tips of the toes,‖ we tapped the digital tendons near the metacarpophalangeal joints, as advised by Kennard and Fulton,[11] and employed a heavy reflex hammer, as recommended by Rittmeister.[6]

RESULTS OF STUDY

Group I.—Of the 2,500 non-neurologic hospital admissions, 63 had Rossolimo signs, an incidence of 2.5%. Tables 1 and 2 list the cases of Rossolimo signs with other neurologic findings and without other neurologic findings respectively. Table 3 summarizes the two tables.

Thus, of the 63 cases with Rossolimo signs, 28, or 44.4% had other neurologic signs, and 35, or 55.6%, had no other neurologic signs. Bilateral Rossolimo signs did not indicate any greater likelihood for the presence of other neurologic findings than a unilateral sign.

Table 4 shows distribution of the Rossolimo sign according to the age groups in the series of 2,500 non-neurologic admissions.

‖ References 8 and 16.

It is interesting to note that the Rossolimo sign did not increase (omitting the 0 to 19 year group) with age. Actually, the highest incidence was in the 20 to 39-year group. The Babinski [40] and Hoffman [41] signs both showed a higher incidence with increasing age. Perhaps the reason for the greatest frequency of the Rossolimo sign in the 20 to 39-year group may be due to the greatest frequency of multiple sclerosis in this age group.[42] Patients with multiple sclerosis probably die before reaching the older age groups; the duration of life was 13 years in the series reported by Carter, Sciarra, and Merritt.[43]

Finkelstein and Kaczyński [4] ascribe the sign to a toxic state of the central nervous system seen in such conditions as appendicitis, pneumonia, and uremia. We found no relationship between the presence of a Rossolimo sign and temperatures above 100 F. A positive blood serology was demonstrated in 7.5% of the Rossolimo signs and in 4.3% of the remainder of the series. In 4.1% of the series the Rossolimo sign was found in association with hypertension; this slightly higher incidence may be due to pathologic changes in the nervous system caused by the hypertensive vascular disease.

Group II.—In the inductee group, 25 had Rossolimo signs, an incidence of 3.3%. In the men between ages of 21 and 39 of Group I, the incidence of the Rossolimo sign was 3%.

Group III.—Of 444 psychoneurotic patients examined, only 4 had Rossolimo signs. In one of these the sign was very slight; one had a bilateral Babinski sign four years previously, at the age of 36, and most likely had multiple sclerosis in addition to his neurosis. Rittmeister [6] found the Rossolimo sign in eight cases of neuroses. However, the total number of cases examined is not indicated, and of these 8 cases, other conditions, such as migraine and epileptic equivalents, were present in some.

Group IV.—Of 354 patients with multiple sclerosis, 57 had Rossolimo signs, an incidence of 16%. Of the 57 with Rossolimo signs, 38.6% were without Babinski signs, and 61.4% were with Babinski signs. Of the 354 patients, 19.7% had Babinski signs without Rossolimo signs.

The disease in 10 of the patients with Rossolimo signs in Group I could be diagnosed as multiple sclerosis. Thus, 16% of the 63 patients in Group I with other neurologic signs had multiple sclerosis. Krabbe and Ellermann [9] found a Rossolimo sign in 8 of 11 cases of multiple sclerosis. Goldflam [2] studied 288 cases of multiple sclerosis and found a positive Rossolimo sign in 81%. (Rittmeister [6] found that Goldflam's figure should be 76%, rather than 81%.) Rittmeister [6] examined 85 cases of multiple sclerosis and found a Rossolimo sign alone in 26% and a Babinski sign alone in 24%; in the initial stages, the Rossolimo sign was more frequent than the Babinski sign. Of 18 definite cases of multiple sclerosis studied by Müller-Neff,[14] 12 had Babinski and Rossolimo signs; 5 had no Rossolimo sign and a positive Babinski sign, and 1 had neither the Babinski nor the Rossolimo sign. Müller-Neff did not agree with Goldflam's statement that the Rossolimo sign is more frequent than the Babinski in multiple sclerosis. The present series of multiple sclerosis cases shows the incidence of the Rossolimo sign not to be as high as that given by Goldflam. We can, however, confirm the value of the Rossolimo sign as an early sign of multiple sclerosis, having followed several cases in which a full-blown syndrome developed in a few years.

Group V.—Goldflam [2] noted the presence of a Rossolimo sign in a small series of head injuries when there was injury to the frontal cortex. He [2] indicated that it may appear before the Babinski sign. This finding is the reverse of Rossolimo's [8] experience that in a pyramidal tract lesion the Rossolimo sign appears about three weeks after the onset of the condition, and later than the Babinski sign. Voss and Meyer [44] found the Rossolimo sign in 23 of 108 cases of head and face injuries sustained in industrial accidents. Although both Prissmann [15] and Markow [1] stated that

TABLE 5.—*Cases of Rossolimo Sign in 2,612 Head Injuries*

Age, Yr.	Sex	Laterality of Sign	Other Neurological Findings	Diagnosis	Interval from Head Injury
40	M	Lt.	Lt. Babinski, rt. KJ > lt.; rt. triceps > lt.; rt. lower facial paresis	Cerebral laceration	17 wk.
54	F	Lt.	Rt. lower facial paresis; rt. Babinski; rt. hyperreflexia	Concussion, postcone. synd.	4 mo.
41	M	Rt.	0	Basilar fracture	8 mo.
28	M	Rt.	Lt. KJ and AJ > rt.	Concussion	5 mo.
24	M	Lt.	Lt. Babinski	Cerebral laceration	4 mo.
41	M	Lt.	Rt. Babinski	Cerebral laceration	9 mo.
50	M	Lt.	0	Posteone. synd.	2½ mo.
45	M	Bilat.	0	Posteone. synd.	27 days
30	M	Rt.	0	Posteone. synd.	7 yr.
9	M	Bilat.	Rt. hyperreflexia; rt. Babinski	Cerebral laceration	5 wk.
26	M	Lt.	0	Posteone. synd.; subdural hematoma (operated)	4 mo.
45	M	Rt.	0	Posteone. synd.	18 mo.
33	M	Bilat.	0	Posteone. synd.	3½ mo.
48	M	Rt.	Weakness rt. lowers; rt. Babinski; rt. abdominals diminished	Cerebral laceration	13 yr.
46	M	Rt.	0	Posteone.	6½ mo.
31	F	Bilat.	Bilat. Babinski; weakness lt. lower; abdominals not elicited; optic atrophy; recurrent weakness rt. lower for 3½ yr.	Posteone. synd; multiple sclerosis	6 mo.
62	M	Rt.	Paresis lt. lower; rt. parietal lobe signs	Cerebral laceration; skull fracture	2¾ yr.
48	M	Bilat.	Bilat. Babinski; weakness and spasticity of lowers; rt. homonymous hemianopsia (weakness in lower limbs antedated head injury by 2 yr.)	Subdural hematoma	10 wk.
44	M	Lt.	0	Posteone. synd.	4 mo.
30	M	Rt.	Rt. Babinski; rt. hyperreflexia; rt. hemiparesis; bilat. VI nerve signs	Cerebral cone.; multiple cranial nerve signs	6 mo.
27	M	Bilat.	0	Posteone.	9 yr.
24	M	Rt.	Rt. hemiparesis; rt. Babinski; mixed aphasia	Posteone. synd.; depressed skull fracture	9 yr. 1 yr.
24	M	Rt.	Rt. hemiparesis; rt. Babinski; mixed aphasia	Skull fracture	4 mo.

the Rossolimo sign appears about three weeks after a head injury, Rittmeister [6] elicited the Rossolimo sign soon after the head trauma; in his series, it was absent at first and positive later in two cases; it was positive, then absent, in three cases, and fluctuated from time to time in three other cases. It was demonstrated in 1 of 15 cases of severe traumatic encephalopathy. He stated that it was rarely positive without other pyramidal tract signs. He implied that a positive sign is not evidence of commotio but is indicative of a circumscribed injury to the brain, especially of the frontal cortex.

Table 5 lists the cases of head injuries with the Rossolimo sign. In our series the Rossolimo sign was present in 23 cases, an incidence of 0.89%. Of the 23 cases, 10

had no other objective neurologic signs, and 13 had other neurologic findings; 1 of the 13 was a case of multiple sclerosis, and another had had progressive weakness of the lower limbs for two years prior to the accident.

SUMMARY AND CONCLUSIONS

The incidence of the Rossolimo sign was investigated in five control groups: Group I, consisting of 2,500 non-neurologic admissions to a general hospital; Group II, of 706 inductees between the ages of 21 and 35; Group III, of 444 psychoneurotic patients; Group IV, of 354 patients with multiple sclerosis, and Group V, of 2,612 patients with head injuries sustained 4 weeks to 19 years prior to the examination.

The incidence of this sign was 2.5% in the 2,500 non-neurologic admissions, 3.3% in the inductee group, 0.9% in the neurotic group, 16% in the multiple sclerosis group, and 0.89% in the head injury group.

The Rossolimo sign occurred most frequently in the age group of 20 to 39, and it did not increase with age as did the Hoffmann and Babinski signs.

The presence of the Rossolimo sign is in favor of organic disease. It occurred with other neurologic signs in 44% of the 63 patients who showed the sign in the 2,500 non-neurologic admission group and in 48% of the 23 patients who showed the sign in the 2,612 head injury group.

Although the Rossolimo sign is frequently found with other pyramidal tract signs, the not uncommon dissociation between the Rossolimo and other pyramidal tract signs favors Goldflam's explanation of the sign as being due perhaps to involvement of an extrapyramidal pathway running from the premotor area of the brain and into the lateral columns.

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Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

Raymond D. Adams, M.D., *President, Presiding*
Regular Meeting, Jan. 21, 1954

Classification of the Myopathies. Dr. John N. Walton.

In a study of natural history and inheritance of a series of 136 cases of myopathy, the cases were first divided into two broad groups, the primary myopathies, or muscular dystrophies, and the myotonic syndrome. If the rare distal, congenital, local, and ocular types are excluded, the muscular dystrophies are seen to consist of three clinically and genetically distinct types. Type I, the Duchenne, or pseudohypertrophic, type is characterized by (*a*) expression almost invariably in males, (*b*) onset usually in the first three years of life but occasionally much later, (*c*) transmission as a sex-linked recessive character with a high mutation rate, (*d*) symmetrical involvement of pelvic girdle muscles and later of the shoulder girdle, (*e*) frequent pseudohypertrophy of the calves, and (*f*) steady and rapid progression, generally leading to death in the second decade but sometimes not until middle life. Type II, the facioscapulohumeral form, is distinguished by (*a*) expression in either sex, (*b*) onset at any age, (*c*) transmission usually via an autosomal dominant gene, (*d*) occurrence of abortive cases, (*e*) involvement first of facial and scapulohumeral muscles, (*f*) rare occurrence of muscular pseudohypertrophy, and (*g*) slow progression with long periods of arrest and survival often to a normal age. Type III, the limb-girdle form, is characterized by (*a*) expression in either sex, (*b*) onset usually in the second or third decade but sometimes in middle life, (*c*) transmission usually via an autosomal recessive character, (*d*) initial involvement of either shoulder or pelvic girdle muscles, with occasional pseudohypertrophy, and (*e*) variable rate of progression, but frequent severe disability and death in middle age.

It is agreed that myotonia congenita, paramyotonia, and dystrophia myotonica are distinct clinically, but much evidence suggests that the three conditions are but variations of a single disease process, which may be called the myotonic syndrome.

DISCUSSION

Dr. D. Denny-Brown: This study is most stimulating, especially in regard to the family history and pedigrees that Dr. Walton has collected. It is remarkable how consistent the type of inheritance of each form of muscular dystrophy turns out to be—much more consistent than any one of the commonly accepted clinical criteria.

Unhappily, the pedigree is not always available in the clinic, and the patient without family history may be a mutant of a dominant, or the only evidence of a recessive, gene. Clinical criteria therefore still have their value.

Dr. James B. Ayer: Is there anything in the cases that ran an atypical course? Is there anything that gives an idea of what made the progression stop? I was disappointed that Dr. Walton did not differentiate a little on anatomical and pathological findings. Do I understand that all types show similar muscle disturbance pathologically, or that some of them show a different picture associated with the muscle degeneration? We are all interested in treatment that has been suggested from California. Has Van Meter's treatment been tried? Wartenberg said he had seen definite improvement, a statement which rather surprised me.

Dr. John N. Walton: Although all the pedigrees of the Duchenne type which I showed tonight revealed a clearly defined sex-linked inheritance, I had, in addition, many isolated cases of the classic pseudohypertrophic type, single ones in a family. This gene has a very high mutation rate. It can arise anew in a family by mutation and produce a large number of single cases.

The myotonia in dystrophia myotonica is usually seen in the hands, forearms, and muscles of the tongue. However, I have had cases in which it was generalized and others in which it could be demonstrated only with the electromyogram.

The pathological changes in muscles are very similar indeed in all types of muscular dystrophy. It is important, however, to distinguish the findings in those cases of so-called menopausal muscular dystrophy, in which the patient is suffering from polymyositis.

We tried five forms of treatment: synthetic tocopherol, mixed natural tocopherol, wheat germ oil, nicotinic acid, and a control. I assessed the results but was not aware which patient had received which treatment. Treatment was continued for six months. At the end of this period I discovered subjective improvement in two or three patients in every group. I could not find objective improvement in any. Just as much subjective improvement occurred in the controls as in the patients receiving supposedly effective forms of treatment. There are papers continually appearing, like that of Dr. Van Meter's, in which the cases and results are poorly documented. All the things in Van Meter's "cocktail" have been given before, without effect. For the present, I should say there is no evidence that there is any effective therapy for muscular dystrophy.

Differentiation of the Various Afferent Systems in the Brain by Anesthesia. Dr. Mary A. B. Brazier.

The author pointed out that in recent years, in many widely scattered laboratories, electrophysiological evidence has been mounting for the existence of some pathways in the brain that have not yet been traced by the anatomist.

For some years her work with human subjects had presented certain paradoxes. She noted the very generally accepted theory of sleep, and also of anesthesia, that in such states of impaired consciousness impulses are being prevented from reaching the cortex; yet the Davises showed in 1938 that there is an electrical response at the cortex during sleep to a stimulus too weak to wake the sleeper. She demonstrated a similar response in anesthesia by slides of subjects under thiopental (Pentothal) anesthesia and under the effects of scopolamine and morphine on stimulation by both sound and light. She demonstrated that whatever the sense modality stimulated the response was not at the specific receiving cortex but in the premotor region (apparently Area 6). There was no observable behavioral response on the part of the patient.

A review was given of the evidence for Forbes's secondary response to a single sciatic stimulus, which follows about 70 msec. after the rapidly conducted primary and appears diffusely in both hemispheres. Slides were shown of a similar phenomenon in the visual system and in the auditory system.

A review was also given of the work from Magoun's laboratory on the responses that travel by the ascending reticular system to the cortex, losing on their way their specificity for the sense modality initiating them. It was argued that these responses are not identical with the Forbes response, since their latency, although longer than that of the primary, was not nearly so long as that of the Forbes response.

It was demonstrated by slides that three responses with discretely different latencies can be evoked in the visual system from a single flash and from the auditory system by a single click, through a careful manipulation of anesthetic level. The second of the three responses had a latency in the range found by Magoun for the pathway through the reticular system. Barbiturate anesthesia at a level that can be defined approximately in operational terms will reveal all three responses. Additional anesthesia in specified moderation has the following differential effects:

1. The primary response is unchanged. 2. The response presumably carried by the ascending reticular system is lost. 3. The long-latency response of Forbes is augmented.

Possible hypotheses were discussed. It would appear that the ascending reticular system needs to be active for the brain to handle (and the subject to be conscious of) the sense-specified signals coming in over the primary system.

DISCUSSION

Dr. Hudson Hoagland: This paper is very interesting, and I should like to congratulate Dr. Brazier on the significance of her contribution. There is something that puzzles me. Of the three responses, the primary cortical response involves the smallest number of synapses, probably only three, and is little affected by anesthesia. The Forbes response, with its long latency and other properties, presumably involves many more synapses. Yet this response actually increases with depth of anesthesia. In general we think of anesthesia as knocking out synaptic conduction, and we might therefore expect to see the Forbes response markedly inhibited.

DR. JEROME K. MERLIS: In the literature one sees descriptions of many different electrical responses to afferent stimulation, e. g., recruiting, secondary, irradiating, diffuse, repetitive, augmenting, K-complex, etc. The conditions of the experiment vary considerably, and it becomes more and more difficult to determine which responses are being described under different names. Does Dr. Brazier believe that the brief latency responses she has described correspond with any of the responses previously described under another name?

DR. RAYMOND D. ADAMS: The implications for clinical neurology are far-reaching. In states like sleep, in which we have assumed that the activity of the cortex is in abeyance, it is clear now that the cortex is responsive. This finding would suggest that suppression of consciousness in the form of sleep or anesthesia is a suppression of certain sensory systems and not others. Dr. Brazier's work is a very significant step forward in an investigation, which I am sure she will continue, in relation to the different clinical states we see in anesthesia and sleep. Do analgesic drugs have different effects on this triple sensory response than do the soporific drugs? We have in our hands a means of studying the effect of a number of different agents on the nervous system.

DR. JOSEPH M. FOLEY: Does Dr. Brazier think the Forbes response is extralaminal as well?

DR. MARY A. B. BRAZIER: In response to Dr. Hoagland, there is some evidence, mostly from the work of Magoun's group, that the brain stem acts as a balanced inhibitory and activating system. My hypothesis, which I have been trying to test, is that at this level of barbiturate anesthesia the inhibitory system of the brain stem is depressed before the activating one. There is some evidence from other laboratories that might tie in with that idea, i. e., from the work of Dr. Kerr in Los Angeles, and of Dr. Lindblom at the Karolinska Institute, in Stockholm. People have been familiar with inhibiting action descending from the brain stem. These two workers have brought out evidence of inhibition of ascending impulses.

In reply to Dr. Merlis, I think it unlikely that the second response, of brief latency, that follows the primary can be related to any of the repetitive phenomena he mentions, since Magoun has shown it to have a very long recovery time.

In reply to Dr. Adams, I have no experience with analgesics other than morphine. I agree the field is a fruitful one to work in. I might mention that one does not get these responses in ether anesthesia.

In reply to Dr. Foley's question about the Forbes secondary response, Morison and Dempsey concluded that there was a thalamic and an extrathalamic route. They demonstrated two levels at which impulses cross—at the level of the superior colliculus and in the anterior third of the corpus callosum.

Epilepsy as a Sequel to Cerebral Vascular Disease: A Clinicopathological Study. DR. PHILIP R. DODGE, DR. EDWARD P. RICHARDSON JR., and DR. MAURICE VICTOR.

Despite voluminous literature concerning both epilepsy and cerebral vascular disease, relatively few well-documented cases are recorded in which epilepsy has appeared as a result of cerebral vascular lesions, and it is often thought that epilepsy is very rarely seen as a complication of such lesions. We should like to call attention to an important and often overlooked cause of recurrent seizures in adult life.

In the clinicopathological study of six cases of recurrent seizures with cerebral vascular lesions, the ages ranging from 46 to 75 (average 59) years, seizures were the most striking neurological manifestation in four and were the only evidence of cerebral disease in two; in two there was serious neurological deficit along with the seizures. The seizures were focal, or had focal aspects, in all, but four patients had generalized attacks as well. Although a remission from attacks of four and a half years occurred in one, seizures continued at variable intervals for the remainder of the other patients' lives. Pathologically, all had old infarction of the cerebral cortex, in the Sylvian and Rolandic regions. The infarcts were embolic in five and secondary to thrombosis of an internal carotid artery in one.

The frequency of epilepsy with vascular lesions, in a survey of a year's autopsy material, was found to be 5.8% (6 cases) of 104 cases of grossly visible cerebral infarction or hemorrhage, as compared with 1.3% (1 case) of 74 cases of cerebral atherosclerosis of similar mean age without such lesions. With exclusion of recent lesions, epilepsy occurred in 6 of 22 cases of old

cortical infarction and in no case in which the cortex was not involved. The importance of this form of epilepsy is emphasized in order that hazardous diagnostic procedures be not undertaken in this group without careful study and consideration.

DISCUSSION

DR. RAYMOND D. ADAMS: I have watched Dr. Richardson, Dr. Victor, and Dr. Dodge collecting these data and have discussed their findings from time to time. Their study has been instructive to me. Vascular disease seldom is the cause of recurrent seizures. When such a case presents itself, one should consider tumor or trauma and only by exclusion make a diagnosis of vascular disease. This work throws this teaching into serious question. It seems to me that one is forced to accept the notion that if vascular disease does involve the cerebral cortex, it is as likely to cause seizures as a traumatic lesion. I do not suppose Dr. Richardson would like to have us conclude that every case of seizures in an older age group represents vascular disease, but he and his co-workers have evidence to show that vascular disease is as important a cause of tumor, and in the late age group probably more important. Why was embolism so high in the causation of this type of syndrome? The answer is that embolism is more likely than thrombosis to cause cortical lesions, although with carotid artery thrombosis there may occasionally be multiple scattered foci of cortical infarction.

DR. JAMES C. WHITE: I do not think any neurosurgeon who has written about epilepsy has given consideration to the possibility that it may be due to cerebral vascular accidents. When a man in middle life develops epilepsy without history of previous cerebral trauma or infection, the burden of proof is on showing that he does not have a brain tumor. This is naturally the neurosurgeon's first thought. It is very valuable to us to have it pointed out that seizures may also arise as sequelae to vascular accidents.

DR. A. POPE: Could the marginal zone of cortex at the border of the infarcted area be differentiated histologically in the cases in which seizures developed, as compared with those in which they did not? Was there any pathological evidence in the epileptogenic lesions for a progressive destructive process of the sort described by Dr. Penfield in meningocerebral scars?

DR. RANDOLPH K. BYERS: In our follow-up study of children with cerebral palsy we have been struck by the frequency of convulsions in children with hemiplegias. These have occurred apparently in both the congenital and the acquired group of hemiplegias. In the children with acquired hemiplegias, since we have been doing arteriograms, we have found that a fairly large percentage have vascular occlusion, the middle cerebral artery being involved in some of its branches in most of them. Of these children, many went years before having convulsions. Others had convulsions for a period and the seizures stopped spontaneously. One thing, however, is striking: If the children with convulsions are separated from those without, intellectual development of the children with convulsions is poorer than that of the other group. Whether this means that a more widespread lesion of the brain has occurred in those who develop convulsions and whether this interferes with intellect, or whether the convulsions themselves interfere with intellectual development, we do not know.

DR. ROBERT S. SCHWAB: Was there any relationship between seizures and presence or absence of hypertension? Were there any cases with the lesions in the occipital lobe or the frontal pole?

DR. HAROLD W. WILLIAMS: I agree that epilepsy may be a sequel to cerebrovascular disease. I should like to expand the concept of "Epilepsy as a Sequel" to the concept of recurring patterned episodes. I think of the 82-year-old patient who has had some eight recurring episodes of aphasia and right-handed weakness of one-half hour's duration. In another instance, Dr. Hamlin's case, there were episodes of Ménière's syndrome, recurring over a period of 14 years. Autopsy showed bilateral occlusion of the posterior inferior cerebellar artery. The histology did not make possible the understanding of how a lesion, essentially static from the neuropathological point of view, can give rise to recurring episodes.

DR. D. DENNY-BROWN: I should like to ask whether Dr. Richardson feels that the hemorrhagic infarct has an epileptogenic influence, particularly since the extravasation of blood in some of these cases seems more than might be expected from arterial thrombosis.

DR. BERTRAM SELVERSTONE: Has Dr. Richardson found, especially in the smaller lesions, any noticeable enlargement of the ventricle on the side of the lesion?

DR. EDWARD P. RICHARDSON JR.: Dr. Pope asked about the marginal area at the border of the infarct. We see abnormality in the immediate vicinity—the nerve cells are thinned out there—but we have not been able to detect any differences in the pathological appearance of that region in the cases associated with epilepsy and that in other cases of infarction without seizures. We found nothing we could interpret as a continuing or progressive lesion. The cellular appearance was characteristic of a quiescent lesion in which all activity had subsided.

In connection with Dr. Byers' remark about children with cerebral lesions and epilepsy, several of our patients remained normal mentally. In this group, in the later adults years, we think that the effect on intellect has chiefly to do with the size and location of the original lesion.

In answer to Dr. Schwab, hypertension was not a significant factor in the group with seizures, but we arbitrarily excluded "hypertensive encephalopathy" from our series because we think that it presents a special problem in cerebral vascular disease that should be considered separately from the lesions under discussion. In one case of recurrent seizures in the large series, the grossly visible infarction was in an occipital lobe, but there were, in addition, multiple microscopic infarcts in other areas of the cortex.

Dr. Denny-Brown asked about the possibility of greater epileptogenic properties of hemorrhagic infarction as compared with ischemic infarction. It is difficult to answer that question exactly because several of the cortical infarcts we observed were ischemic and others were hemorrhagic. We have not at present sufficient data to answer this question with assurance.

As to whether the small cortical infarcts in the case of carotid artery occlusion could have been embolic, it must be conceded that they may have resulted from the detachment of portions of the thrombus in the carotid artery. We cannot be certain about this point.

In answer to Dr. Selverstone, we had a pneumoencephalogram on only one case, and that patient died, apparently as a result of the procedure. Nothing abnormal could be detected in the films. The original cortical infarcts were so small that there was no significant ventricular enlargement.

Walter Wegner, M.D., President, Presiding
Regular Meeting, Feb. 18, 1954

Conditioning and Emotional Behavior. DR. HOWARD LIDDELL.

Pavlovian conditioning is always difficult for the animal, because through habituation it becomes emotionally muscle-bound and cannot fight back or flee from the emergency situation of the daily conditioning tests. Every positive or negative conditioned stimulus elicits in sheep or goat tense anticipation as to what is to happen next, and this is one manifestation of emotional behavior. The animal is forced to anticipate whether the signal is to be followed by mild shock to the foreleg or not. This emergency preparation with its accompanying emotional behavior can be made still more stressful by imposing a rigid time schedule in which 10-second signals are separated by equal intervals of time of from two to six minutes. Such training procedures lead inevitably to chronic emotional disturbances (or experimental neurosis, to use Pavlov's misleading designation).

Approaching emotional breakdown is foretold by clearly distinguishable prodromal stages of behavior under continuing stress. Soldiers under combat conditions exhibit the homologues of these same prodromal indicators. However, the stresses of combat may be counterbalanced by indoctrination and effective leadership. The stresses of conditioning are counterbalanced in the lamb or kid 3 to 8 weeks of age by the presence of the mother. This "protective" influence is being experimentally analyzed.

The homologue of "psychic trauma" from solitary early conditioning can be demonstrated when "protected" and "unprotected" kids are subjected once again to the stress of conditioning when 2 years of age. The animals not "protected" by the mother's presence during youthful training succumb sooner than the "protected" animals.

DISCUSSION

DR. WALTER WEGNER: This discussion has been most interesting and stimulating, and I am sure it could have continued much longer. The problems that have been raised and sketched are numerous. These experiments have been going on since 1921, and so in the 33 years that have elapsed Dr. Liddell has passed through the period of dominance of quite a variety of schools of psychology, quite a variety of explanations for what goes on. No doubt each school could interpret the things that happened in a different way and could tell us how they have come about.

DR. STANLEY COBB: If I were to express what these experiments meant to me, it would be a long lecture, and the reason is that I have had an interest in the work of Professor Liddell for years. I have been fortunate to visit him on the farm and see these animals. If you went there, you would think the behavior of the animals was more remarkable than the examples we have had on the screen. I am sure that my whole understanding of the experiments of Pavlov has been changed by watching Dr. Liddell's work. That is for all of us a fairly fundamental change. The main issue, as I see it, is that he has observed the whole animal as an organism; he has observed a large number of factors in the environment, whereas Pavlov, in his earlier work at least, thought that he was isolating the animal and was performing an experiment on the effect of stimulus and conditioning on an animal isolated from his environment. Dr. Liddell has shown us that the isolation itself was a conditioning of the animal. I won't go into that, because others here can speak on conditioned reflexes more authoritatively than I.

I should like to bring up some questions about the emotions. Psychiatrists, neurologists, and moralists often are heard to say that it is "bad" to have emotions and that to have intellectual functions is "good." If your emotions interfere with your intellectual functions, then the emotions are looked on as something inferior. That is a very usual attitude of mind. I should like Dr. Liddell to tell us what he thinks about the emotions from this moralistic point of view and to tell us where the useful reaction of alertness stops and anxiety begins. Is there a line? I should say, even, that a little anxiety is probably useful to a speaker. I was told a number of years ago by Harvey Cushing, one of the best speakers I ever knew, that on entering an amphitheater he always had palpitations, sweating, and tremor. I am skeptical about the idea that to have anxiety is pathological and that emotions are "bad."

DR. HOWARD LIDDELL: In the words of my wife, one talented young lady said, "But what about joy?"

DR. WALTER WEGNER: The remarkable similarity of human beings to animals in the field of their emotional responses is apparent in this presentation. I wonder whether Dr. Liddell may sometimes find himself philosophizing about their common origins, or something of that sort. Because of this remarkable similarity, it would seem that the treatment of neuroses in human beings must find an answer in a continuation of this work. Dr. Skinner's name has been mentioned, and I understand that some work he is doing is a partial answer to that problem.

DR. BURRHUS F. SKINNER: The comment, "What about joy?" was one I wanted to raise myself. What we call "anxiety" is generated by the intermittent, but fairly regular, presentation of a noxious stimulus. It is one of the more important clinical emotions. The responses Dr. Liddell studies are pretty much unconditioned disturbances of behavior. They are not behaviors which he sets up in particular form. They are the "wringing of the hands" of the sheep. I am more interested in what noxious stimuli do in interfering with the regular business of the day. The anxious business man is possibly wringing his hands and pacing the floor, but he is also not paying attention to business. I am interested in knowing why he cannot pay attention to business rather than why he shows certain spontaneous manifestations of emotion. My own techniques try to show how an anxiety-producing stimulus suppresses stable behavior already in progress.

The really traumatic effects of emotion, as Freud exposed them, seem to be concerned not with the expression of emotion at all but with by-products of the attempt to conceal emotion. His first case, I believe, was that of a girl whose hysteria appeared to be due to an attempt not to show emotion at the bedside of her father. I should like to ask Dr. Liddell, "Have you tried to control the expression of emotion in sheep and, if so, what are the results of such control?"

DR. WILLIAM MALAMUD: It seems to me that this excellent presentation by Dr. Liddell warrants more discussion than has been raised so far. Personally, in my contacts with Dr.

Liddell I have been particularly interested in his ideas about the application of the work that he has done to the teaching of medical students. I remember discussing with him the possibilities of presenting to first-year medical students the results of his findings in the attempt to introduce the study of human behavior through a psychobiological approach, as he presented it tonight. It is a difficult thing to do, and I felt that his ideas were most stimulating. I was wondering whether Dr. Liddell could tell us more of how one could use this approach in a course on human behavior in the first year of medicine. Would Dr. Liddell elaborate on such a plan?

DR. G. COLKET CANER: Was any attempt made to give these animals more security by petting them? I understand that in cases in which emotional disturbances developed they lasted indefinitely. Was that true of all animals?

DR. ROBERT S. SCHWAB: Are other systems involved in these animals? Do they get ulcers, lose their appetite, etc., beside having tachycardia and rapid breathing?

DR. WILFRED BLOOMBERG: I have two somewhat philosophical problems that bother me. One of these is in terms of the description of this approach as "psychobiological." Actually, if this approach were applied to human beings instead of to sheep, it would be described not as psychobiological but as "behavioristic" in that it ignores not only the psychodynamic implications but all the constitutional implications that have been lumped under the general group of "instincts." I wonder how this purely behavioristic approach correlates with the instinctive drives and with what in the human might be called the psychodynamic interpretations.

The second point was touched on by Dr. Cobb's opening discussion, but I still feel the need to amplify it. This is the matter of what appears to me to be the insertion of value-judgments. Dr. Liddell says that "one kid is protected and another deprived," and he further describes an alertness which becomes a disturbed alertness. It seems to me that it is a value-judgment to say that the "protected" kid, which moved freely around the room, was acting more "normally" than the unprotected, "deprived" kid, which clung to one wall. It may be that for a normal sheep, or kid, not subjected to electric shock moving freely around the room is a more normal behavior, but it may also be that for a kid subjected to electric shock keeping to one wall is a more adaptive, and therefore more suitable, behavior than to wander around the room. It disturbs me to see incorporated in these conclusions, therefore, what I consider value-judgments by characterizing certain behavior without justification as "better" or "worse." I wonder whether Dr. Liddell would amplify some of these things in terms of interpretation. I think we either should be behaviorists completely or should explain our value-judgments more clearly.

DR. JOSEPH M. FOLEY: Professor Liddell's terminology and liberal use of analogies appear to beg the question of the relationship of experimental neurosis in animals to emotional disorders in man. Therefore I should like to ask whether Professor Liddell would define what he means by emotion?

DR. WALTER WEGNER: I should like Dr. Liddell to define neurosis also.

DR. HOWARD LIDDELL: The philosophical problems that bother Dr. Bloomberg and Dr. Foley cannot be disposed of categorically. They are problems as bothersome to the investigator of animal behavior as to the clinician. I do not believe that we have made a liberal use of analogies and thus begged the question of the relationship of experimental neurosis in animals to emotional disorders in man. The emotionally disturbed sheep is not "anxious" and does not suffer from "insomnia" in the clinical sense. It does, however, if one examines its behavior in barn and pasture, exhibit the homologues of anxiety and insomnia. The zoological principle of homology need not be limited to such structures as the sheep's foreleg and the human hand and arm. The ethologists, Lorenz and Tinbergen, as well as myself, believe that there are homologous behavior as well as structures. It is these homologous behaviors in sheep and man that we are seeking to decipher in order to disclose the animal origin of Freudian psychodynamics. Pavlov was guilty of employing analogy in his use of the term "experimental neurosis." There is no need to say more than that the animals following difficult and prolonged conditioning exhibit chronic states of emotionally disturbed behavior. If dogs enter the pasture and a "neurotic" sheep runs in one direction and the rest of the flock in another, the dogs may kill this sheep. Its behavior in this crisis is emotional, and its normal relations with the flock are disturbed. We have discovered in such sheep that these relations with the flock are chronically disturbed.

In our studies of animal behavior we employ value-judgments in precisely the sense that clinicians employ them. For example, we say that a "good" goat mother "protects" her kid from

the dangerous stress of conditioning by her presence during the test hour. Each value-judgment is based upon surmise or intuition as to the outcome when not so "protected" in terms of the kid's subsequent growth and development, i. e., its survival. The value-judgments invoked here raise specific problems for experimental analysis. What is a good mother? How, in detail, does she protect her kid by her presence during stressful training? These questions we are presently attempting to answer by experiment.

We have been unable to reassure our sheep and goat subjects by our presence during training. On the other hand, petting and reassurance are efficacious in the case of the dog, as shown by Dr. W. Horsley Gantt. Typically, the emotional disturbances of our animals last for life.

As for organ dysfunction in the disturbed animals other than that of the heart and lung, we typically observed excessive micturition and defecation during the laboratory tests.

In reply to Dr. Malamud, during the past 10 years we have demonstrated our animals to medical students. By listing on the blackboard the animal's repertory of conditioned stimuli, positive and negative, we bring our "patient" before the class for presentation. The students may then ask the patient questions by instructing the demonstrator as to which conditioned stimuli they wish the animal to respond. Within the hour most medical students begin to see the animal's presenting behavior as a product of its past laboratory training. The impact of two or three such case presentations of an animal in the place of a patient will suffice to sensitize the student's powers of observation with respect to these simple episodes of behavior. It is unnecessary and undesirable to burden the medical student with another textbook and another course of lectures in order to achieve our modest educational objective.

I fully agree with Dr. Cobb in his skepticism concerning the usefulness of moralizing about emotion. In our opinion there is no such thing as unadulterated thinking or unadulterated emotion.

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND THE NEW YORK NEUROLOGICAL SOCIETY

Morris B. Bender, M.D., Secretary, Section of Neurology and Psychiatry, Presiding

Joint Meeting, Jan. 12, 1954

Use of Psychotherapy for Seriously Disturbed Patients. Dr. William K. McKnight (by invitation).

The application of various psychotherapeutic techniques in the treatment of patients who are seriously disturbed and most effectively treated in the hospital setting was presented and summarized from a study of clinical material representing a series of 20 patients under treatment at the New York Hospital-Westchester Division.

A comprehensive bibliography was referred to in evaluating various psychotherapeutic objectives, and the continued need for further understanding of therapeutic goals was discussed. Emphasis was placed on the desirability of utilizing present knowledge of psychotherapeutic principles in a more widespread manner while further research is carried on and of utilizing such techniques to help patients to relate to reality situations with improved motivation and in increasingly effective ways through periods of disturbed behavior. Careful diagnosis and dynamic study, the judicial use of group and cultural facilities within the hospital environment, and the use of electroconvulsive treatment, when indicated, were related to individual psychotherapy, which is based on the development of a flexible, individualized physician-patient relationship, utilizing suggestion, reeducation, directive control, interpretation, and support. Combined with appropriate physical and nursing care, as well as with detailed analysis and gradual modification of contributory or complicating family attitudes, a psychotherapeutic approach, as described, is found to enable the patient to gain maximum hospital benefit and to achieve through his hospitalization a meaningful and constructive experience, leading to a more stable personality adjustment.

DISCUSSION

Dr. Robert B. McGraw: I should like to underline some of Dr. McKnight's remarks which struck me as significant and important. They are as follows: "In respect to the background the underlying maturity of the human personality must be gauged in the final analysis not

solely in terms of freedom from crippling anxiety and fear, but by the achievement of a sense of personal and social values which is compatible with the basic biologic characteristics of the individual." Then, further: "The methods by which the therapist through his personality applies the theories and projects of scientific research constitute the art of medicine and, as such, become the definitive source of psychotherapy. . . . The combination of good physical care, nursing attention, and medical treatment with psychotherapy provides the best opportunity for clinical response."

In respect to the details of treatment, which is a matter that many therapists find most difficult to record and relate to others, to their colleagues particularly, either by word of mouth or by written note, I think that Dr. McKnight has been able to give these rather well. He says: "This procedure provides the patient with an orientation of the therapist's scope of interest and creates a beginning frame of reference as to the significance of experience and personal values." I found myself in very general accord with the methods described.

Intensive Dynamic Psychotherapy of Depressions. Dr. Richard N. Kohl (by invitation) and Dr. Frederic F. Flach (by invitation).

During the past three years, investigators at the Payne Whitney Psychiatric Clinic of the New York Hospital have studied depressed patients with a generally poor prognosis and have found that they may respond favorably to intensive psychotherapy when carefully selected and treated under optimal circumstances. Some degree of success in the patient's preillness life adjustment and the full cooperation of his responsible relatives are considered to be important criteria of selection. Uninterrupted treatment within a hospital affords protection, planned activities, control of dynamically significant environmental factors, and careful observation of psychopathologic changes. Electroconvulsive therapy may be used as an adjunct to psychotherapy for the purpose of eliminating those symptoms which seriously interfere with progress. The goal of treatment is not merely recovery from the immediate depression but is the prevention of further recurrences of the illness.

Since preventive treatment and deep analysis of manic-depressive reactions are generally considered to be of little or no value, a patient of this type was selected for treatment as outlined above. Various therapeutic techniques, including free association and dream analysis, were utilized in the investigation and analysis of his clinical elations and depressions. Treatment continued without interruption during exacerbations and remissions of his symptoms. When the patient recovered from his depression, intensive psychotherapy was directed specifically toward the modification of those personality features which he recognized as potential sources of future depressions.

DISCUSSION

Dr. S. Bernard Wortis: I cannot help but feel that many of my remarks will identify me as a B. C. (before convulsions) therapist. The present-day tendency of some therapists to shock patients first, and to find what ails them later, is a sad commentary on our times. Equally sad is the patient who has been treated outside a hospital with such intensive psychotherapy that the patient injures himself, while the psychiatrist is concerned with the more microscopic dynamics of the illness. I speak of this feelingly because those of us who are on acute hospital services see such patients admitted. The authors of this paper speak of therapeutic results in terms of "prognosis for life" after adequate psychotherapy. Data regarding the long-term effects of intensive treatment of such patients are urgently needed.

Another point comes to my mind: The authors say that the electroshock therapy may be used at the termination of intensive psychotherapy, when the patient has gained adequate insight but still faces a prolonged state of mild depressive convalescence. My question is, "Why give electroshock therapy if the insight is adequate after intensive psychotherapy?"

Dr. Oskar Diethelm: The treatment as carried out by Dr. Flach and supervised by Dr. Kohl may at present be considered as research. I agree with Dr. Wortis. There are some patients I treated in 1929 with a moderately intensive psychotherapy who have remained in good health ever since. On the other hand, as, unfortunately, most of you know, every year there are a few reports of former patients who have terminated their lives in suicide. The longer you live, and the larger practice you have, the more cases like this you get.

The next point involves a statement which has always interested me, one that Freud made in the introduction to his book on dreams, in which he quoted from Griesinger's third edition of his textbook (1871), stating that in dreams and in psychosis wish fulfillments and dynamic factors are clearly revealed. I felt we should at least see whether we could not get some better understanding by aggressively analyzing patients when they suffer a great deal, at the period when we usually are taught not to push too much.

DR. RICHARD N. KOHL: It is true that the patient recovered from his depression, but those features of his personality which dynamically contributed to his illness persisted throughout that period of relative well-being. At the present time the goal of treatment is to alter these features sufficiently to prevent a recurrence of the illness.

Sophocles Contra Freud: A Reassessment of the Oedipus Complex. DR. IAGO GALDSTON.

The most distinguished and original element in the Freudian system is that of the Oedipus complex. Freud considered it his unique discovery. However, he misread the tragedy of "Oedipus Rex" and drew certain psychological lessons therefrom which are not there.

Freud based his elaborate deductions on only one of the three plays Sophocles wrote on Oedipus. "Oedipus Rex," however, mirrors but a portion of the "crimes and punishment of the House of Labdacus." The incest of Oedipus was in effect the midpoint of the tragedy. It was consequent to the crimes of his parents.

In "Oedipus Rex," Freud saw what he took to be a universal phenomenon, the desire of the young child to have incestuous relations with his mother and to destroy the father who stood in the way. On this assumption Freud built an intricate superstructure involving the so-called castration fear, the resolution of the Oedipus complex, the flowering of the superego.

Patricide and incest are heinous crimes. But the burden of "Oepidus Rex" is the utmost depths of degradation to which the son may be reduced by the father unmindful of his moral obligations. The patricide and incest of Oedipus were not *his* crimes, but the dire consequences of the guilts of his parents.

There is nothing in "Oedipus Rex" to justify Freud's contention that the play expounds the universality of the infantile incest wish. It teaches another lesson—one that reflects on the father rather than the son, that has to do with moral fortitude, love, charity, and mercy, rather than with sexuality and infantile incest longings.

Yet it was Freud who linked the Sophoclean tragedy with the dynamics of the child's psychic growth. The Oedipus myth embodies the concept of the paternal matrix within which the nascent personality of the child is nurtured. Where there is love between the parents which yet includes the child, the child will effectively meet the challenges of its maturation and have reciprocal affection for the parent. But where the parents are immature and neurotic, the child might suffer. It is this simple, yet vital, validity that lies at the core of the Oedipus myth, and not the fancied incest wish of the child.

DISCUSSION

DR. GREGORY ZILBOORG: First of all, Dr. Galdston has done himself an immense injustice. He started out extremely well and proceeded from ancient tradition to that which has not been foreseen by Freud in the psychological sense, and this is the tradition that the sins of the fathers are visited upon the children. It is undoubtedly a point of immense importance, a point to which psychoanalysis, as it is presented today, has not given proper clinical consideration.

I should like to ask Dr. Galdston to make one correction when he sends his paper for publication. He refers to incest as a derivative punishment. What he wishes to show is the derivative crime from which punishment was derived, because incest itself is not a punishment, but it becomes a punishable crime only insofar as it is objected to by the father.

DR. IAGO GALDSTON: What Dr. Zilboorg said deserves consideration. One has to read Freud with an eye "agin" Freud; that is, one must use a kind of interpretative screen. But I am sure Dr. Zilboorg is wrong if he thinks that Freud revised his ideas on the Oedipus complex in any way whatsoever. I was very careful to draw the quotations I cited from the latest of Freud's published works, from the "Outline of Psychoanalysis," which he published shortly before his death.

PHILADELPHIA PSYCHIATRIC SOCIETY

Margaret DeRonde, M.D., President, in the Chair
Regular Meeting, March 12, 1954

Interdisciplinary Research in Use of Oral Pentylenetetrazol (Metrazol) in the Psychoses of Senility and Cerebral Arteriosclerosis. DR. MAURICE E. LINDEN, Norristown, Pa., and DR. DOUGLAS COURTNEY.

The authors reported the design and results of one and one-half years of research with pentylenetetrazol (Metrazol) in a variety of psychiatric conditions in the senium. The research population consisted of institutionalized women, of an average age of 76.6 years. Proceeding on the pharmacologic premise that pentylenetetrazol is an analeptic drug with three pronounced modes of action—(1) central nervous system excitant, (2) cardiorespiratory stimulant, and (3) indirectly, incitant of improved pulmonary ventilation, accelerated blood flow, and increased cerebral oxygenation—the drug was administered to the experimental group in 0.20 gm. doses three to five times daily with thiamine chloride, nicotinamide, and ascorbic acid supplementation. A matched control group received the vitamins alone. The following areas of observation were established as a preexperimental base line, at intervals during the administration of the experimental variable, and at the end of the experiment.

I. Physiologic: Complete blood cell count; fasting blood sugar, total protein, urea nitrogen, and icterus index; complete urinalysis; EEG; ECG; T.P.R.; B.P., sleep habits, and physical examination.

II. Psychologic: Rorschach, Wechsler Memory Scale, and Bender-Gestalt.

III. Psychiatric: Psychiatric nurse's evaluation form, psychiatrist's evaluation form, observations of nonpsychiatric physician, and patients' self-evaluation form—all arranged as five point rating scales.

None of the observers, save the psychiatrist project director, knew the identities of the experimental and control groups. Hence, it was felt that a high order of objectivity was attained.

The prediction was made that the analeptic drug, were it effective, would improve thinking processes, orientation, memory, alertness, and the feeling of well-being. The feeling of well-being was dissected into its hypothetical parts, which were the observational areas in all the testing instruments.

After statistical compilation, the data were evaluated for changes, trends, and significances. These findings were further compared with clinical observations. It was found that the patients of the experimental group changed in the desired direction in all the observed areas. While those of the control group improved also, the changes in the experimental group were considerably greater. With the exception of the psychiatrist's observations, none of the changes found were statistically significant in themselves. Since the psychiatrist knew the identity of the patients, his observations may have been somewhat less objective. However, it is probably significant that all the correlated and uncorrelated tests showed change in the desired direction. No toxic effects of the drug were found.

Since there are many factors which render such a study impure, such as the rate of stomach absorption, kidney competence, and cerebral degeneration in this group of patients, and also since these patients improved during a period in which they would normally be expected to get worse, it is concluded that pentylenetetrazol is probably a useful drug in the treatment of the psychoses of great age, both because it improves the patient's general well-being and because it releases psychic energy which can be channeled into a well-formulated treatment program, thereby secondarily permitting use of specific and general psychotherapies.

DISCUSSION

DR. MICHAEL FINN, Baltimore: At Maryland State Hospital we have made a study similar to Dr. Linden's, with approximately the same results; i. e., psychological tests showed much less change than did the social behavior. Most existing tests are not too helpful, the best being the Bender-Gestalt. The Wechsler Memory Scale and Rorschach tests were much too hard for our patients. In general we are for projective rather than expressive techniques. The most

important observation is the clinical improvement, and this is not always associated with improvement in psychological tests. Do you find anything to show a correlation between improvement and personality type?

DR. MAURICE E. LINDEN, Norristown, Pa.: The Goldstein-Scherer test is designed specifically for this age group. In our experience the Wechsler Memory Scale was not very helpful. When elderly patients come into the hospital, it is practically impossible at first to tell advanced dementia from acutely confused senile types. We begin to make a differentiation in group therapy, and on the basis of transference reactions we have separated a number of types which have a disease-specific pattern.

DR. WILLIAM E. KELLY, Philadelphia, Pa.: How important are the vitamins in this program, and which are the most useful? I believe Selye considers that nicotinic acid is one of the best generalized "stressors." Was nicotinic acid used in your series?

DR. MAURICE E. LINDEN, Norristown, Pa.: Selye suggested nicotinamide alone as a valuable supplement, but this is not as good as the two combined, or even as good as pentylenetetrazol alone. The two groups were getting the same amounts of both substances. We found it valuable to combine vitamins, especially massive doses of vitamin B_{12}. We watched another group and found that the patients increased their intake of food on 75 γ of vitamin B_{12} a day. They did not seem to show much improvement otherwise, for instance, psychologically.

DR. ERWIN R. SMARR, Philadelphia, Pa.: Has it been established that these doses of pentylenetetrazol produce a significant increase in cerebral blood flow?

DR. MAURICE E. LINDEN, Norristown, Pa.: I do not think this has been proved. Dr. Seymour Kety has done some work on a small series which showed that the oxygenation was increased.

Margaret DeRonde, M.D., President, in the Chair

Regular Meeting, April 9, 1954

Preliminary Remarks on Group Experiences at Patient Conferences: A Study of the Dynamics in a Multidisciplined Graduate Group. DR. JESS V. COHN and MR. HAROLD J. SMOLINSKY.

A group found itself organized as a team by virtue of common intellectual goal-direction, common professional goal-direction, and common personal emotional needs—organized through automatic and spontaneous association under the aegis of a leader whose symbolic significance was rather quickly amortized out in preference for his real values. This graduate group of hospital employees, who operated in the setting of patient conferences or seminars, developed a wholesome autonomy and confluent unity, particularly because the participants were not (artificially) engineered by hospital administrative needs into their group relationships, and because requirements for such an association were permitted the liberty of self-expression and subsequent sanction into the development of a program presently considered indispensable to the maintenance of standards.

The development of the program and the methods used in the program were detailed, serving as the reticulum, or binding fabrication, for the mellowing of the group cohesiveness. Analogy was drawn between the significance of the several etiological facets in the production of illness and the significance of the same considerations in the production of health, individual and collective, the whole to serve as a frame of reference for discussion that would lead toward an understanding of the mechanics involved in interpersonal actions and reactions at the group level —together with interactions between individual components and the leader, and between the group as a whole and the leader. The entire presentation dealt with the structure and functioning of a group of psychiatric and related personnel on the graduate plane and suggested inferences (derived from this study) that are applicable to similar learning situations on the undergraduate plane.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Anatomy and Embryology

QUANTITATIVE STUDY OF THE BRAIN OF A DEAF-MUTE. V. W. D. SCHENK, Rev. neurol. **89**:208, 1953.

A quantitative examination was made of the eighth nerve nucleus, the superior olive, Henschl's convolution, and the superior temporal and angular gyri of a 65-year-old man who had been a deaf-mute all his life. It was found that the ventral cochlear nucleus of the deaf-mute had a reduced number of cells even in comparison with the cells of a deaf subject. However, the superior olive of the deaf-mute had more cells than that of a deaf subject. The number of cells (1.01 per square millimeter) in the cortex of the transverse temporal gyrus of the deaf-mute was considerably less than normal. In the angular gyrus the number of cells of the deaf-mute was 800.01 per square millimeter, as compared with a value of 700 to 1,200 in normal subjects. In the angular gyrus there was a diminution of the cells of the superficial layers.

BERLIN, Mount Vernon, N. Y.

Physiology and Biochemistry

INHIBITION OF BRAIN HEXOKINASE BY ADENOSINEDIPHOSPHATE AND SULFHYDRYL REAGENTS. A. SOLS and R. K. CRANE, J. Biol. Chem. **206**:925 (Feb.) 1954.

Brain hexokinase, free of interfering enzymes, is inhibited competitively by adenosinediphosphate with respect to adenosinetriphosphate. The enzyme has the same apparent affinity for both nucleotides. Free sulfhydryl groups on brain hexokinase seem to be required for activity. The enzyme is sensitive to heavy metals and is protected by metal-binding agents.

PAGE, Cleveland.

EFFECT OF CORTISONE ON THE URINARY EXCRETION OF 17-KETOSTEROIDS IN PATIENTS WITH CUSHING'S SYNDROME. J. W. JAILER, J. LOUCHART, J. J. GOLD, and A. I. KNOWLTON, J. Clin. Invest. **32**:449 (May) 1953.

It is generally agreed that the manifestations of Cushing's syndrome are due to excessive 11-oxygenated corticosteroid secretion by the adrenal cortex, although the pituitary and the hypothalamus, as well as the adrenal, have been postulated as the site primarily involved.

If either an adrenal or a pituitary tumor is present, it would seem reasonable that the source of excessive secretion responsible for the disease picture would lie in the neoplastic tissue, and in such patients, because of the autonomous nature of the tumor, no fall in 17-ketosteroids would be anticipated following the injection of exogenous cortisone. On the other hand, if no tumor exists, the bilateral adrenal hyperplasia may arise *de novo* and be independent of pituitary control, or the normal pituitary-adrenal interrelationship may still be operating. If the latter obtains, then the administration of cortisone should result in a fall in the 17-ketosteroid excretion.

Jailer and co-workers describe the responses in urinary 17-ketosteroid excretion of six patients with Cushing's syndrome during four to five days' administration of large doses of cortisone.

No alteration was observed in the abnormally high excretion of 17-ketosteroids in one patient with a metastatic adrenal tumor. Significant decreases in 17-ketosteroid levels were noted in five patients with proved hyperplastic adrenal cortices.

ALPERS, Philadelphia.

Diseases of the Brain

AN EXTRACRANIAL MENINGIOMA WITH NO APPARENT INTRACRANIAL SOURCE. E. P. PENDERGRASS and J. W. HOPE, Am. J. Roentgenol. **70**:967 (Dec.) 1953.

Pendergrass and Hope report a single case in which a hard tumor appeared about one month after a blow on the left forehead. The tumor grew slowly, and roentgenograms of the skull five years after the injury showed a diffuse area of increased bone density with some areas of rarefaction in the left frontal area. The abnormal area of bone crossed the midline to the right and extended backward on the left lateral side of the frontal bone. A left frontal craniectomy was performed to remove the bone tumor. The tumor appeared to originate on the anterior side of the frontal bone, and there were no adhesions between the frontal bone and the underlying dura mater. The underlying cortex of the brain appeared normal. At operation the tumor was thought to be an osteoma, since there was no suggestion of communication with the meninges The histologic diagnosis, however, was that of meningioma.

An interesting aspect of the case is the fact that the mass on the forehead had been present for four years and then began to grow larger. At the same time the patient began to notice deafness, which was more pronounced in the left ear, and weakness of his left hand and the left side of his face. Neurologic examination revealed a flaccid paralysis of the extensors of the left hand and left side of face, bilateral deafness, more pronounced on the left side, slight paresis of the extensors of the left forearm, and slight paresis of the left lower extremity. The neurologic symptoms and signs were not explained at the time of surgical procedure and never were explained subsequently. The patient was uncooperative in submitting to further examination. Two years later his neurologic findings were unchanged. He died 10 years after the craniectomy, and no autopsy was obtained.

WEILAND, Grove City, Pa.

A CASE OF GUMMA OF THE BRAIN WITH HYPOTHALAMIC SYMPTOMS. N. RASKIN, Am. J. Syph. **37**:156 (March) 1953.

Gumma of the brain is a very rare manifestation of syphilis of the central nervous system. It produces symptoms not distinguishable from those of any growing tumor. The differential diagnosis may be very difficult, since the blood serologic test may be positive or negative and the spinal fluid normal.

Raskin describes a patient with untreated syphilis of long duration suffering from syphilitic meningoencephalitis and a gumma of the left basal ganglia, causing hypothalamic symptoms, hypersomnia, bulimia, polydipsia, polyuria, and obesity.

The slow progression of the clinical symptoms in this case implies a slow growth of the lesion responsible for their appearance. When the patient was studied 27 years before, the blood test was negative and she had never had treatment for syphilis. She had complained of severe headaches for 20 years, had had an attack of paroxysmal hypertension 8 years before admission, and for the previous 5 years had had numerous nonlocalizing symptoms, due to a space-occupying lesion, and symptoms pointing to involvement of the floor of the third ventricle.

On admission a few weeks before death the blood serum gave a positive serologic test. No lumbar puncture was performed, but the cerebrospinal fluid taken at the time of autopsy gave a negative Wassermann reaction. At autopsy gumma of the left basal ganglia, cerebrovascular syphilitic lesions, and syphilitic meningoencephalitis were found. The gumma came very close to the wall and floor of the third ventricle and by pressure and edema had destroyed the connections of the hypothalamus with the thalamus, thus accounting for hypothalamic symptoms.

ALPERS, Philadelphia.

PROGRESSIVE BULBAR PALSY DUE TO SYPHILIS. R. E. COOK, Am. J. Syph. **37**:161 (March) 1953.

Cook reports a case of progressive motor nuclear involvement of the lower cranial nerves, with bilateral upper motor neurone signs in arms and legs, occurring in a 42-year-old Negro man with positive blood and spinal fluid serologic tests. After treatment with penicillin there was no further progression, and considerable improvement was seen in a two-year follow-up.

While final anatomic proof is lacking, the course, neurological signs, and improvement after penicillin therapy all support the idea that this is a case of progressive bulbar palsy due to syphilis.

ALPERS, Philadelphia.

VALUE OF THE ELECTRO-ENCEPHALOGRAM IN THE DIAGNOSIS OF INTRACRANIAL TUMOURS. S. RENFREW, J. H. CAMERON, and I. L. HAGGER, Brain **76**:92 (March) 1953.

Renfrew, Cameron, and Hagger believe that information from the EEG may be "confirmatory" or "additive" in the case of intracranial tumors. The value of the former is thought to be self-evident; that of the latter depends on the degree of insecurity of the physician. In lateralizing and locating tumors the EEG serves oftenest as a means of confirming clinical opinions (40 to 50% of intracranial tumors) or as a means of planning ventriculography or of checking the results of angiography (12% of intracranial tumors). In determining the organic nature of brain disease and the type of pathology, the value of the EEG remains to be assessed.

In the series of 56 cases of supratentorial tumors (excluding those of the pituitary) the authors found abnormal records in 94.5%, "confident" lateralization in 74.5%, and "confident" localization in 65.4% (figures which correspond closely to those of W. A. Cobb).

JOHNS, New York.

LATE RESIDUAL LESIONS OF THE BRAIN CONSEQUENT TO DURAL HEMORRHAGE. C. B. COURVILLE and E. W. AMYES, Bull. Los Angeles Neurol. Soc. **17**:163 (Dec.) 1952.

Courville and Amyes describe two cases of dural hemorrhage. In the first one, a man aged 49 suffered a head injury in a traffic accident. There was immediate, progressive loss of consciousness. Exploratory craniotomy was done and a large left extradural clot was evacuated, followed by failure to regain consciousness, postoperative hyperthermia, persistent coma with right spastic hemiplegia and left hemiparesis, progressive deterioration, and ultimate development of spastic quadriplegia. Death occurred after a survival period of six and one-half months. Autopsy revealed residual lesions in the upper brain stem, with multiple focal softenings associated with generalized gliosis of the left cerebral centrum.

The second case was that of an injury to the left parietal region in a woman of 37 with chronic alcoholism. Two days after injury a large acute right subdural blood clot was removed. A suggestion of seepage from the right posterior cerebral artery was noted in the angiogram. Transitory slow improvement occurred after a series of stellate blocks, followed by progressive development of a decerebrate state. Death occurred six and one-half months after injury. Autopsy revealed cavities in the upper brain stem and softening in the distribution of the right posterior cerebral artery.

This study is concerned with the not uncommon and often fatal intracranial complications of dural hemorrhage and hematoma. The authors point out that, with the exception of the commonest cause of death in these cases, i. e., increased intracranial pressure, and the relatively rare infections, these complications are essentially vascular in nature. Pressure on the underlying cortex, with variable degrees of damage to this structure, or occlusion of one of the larger cortical vessels with focal cortical and subcortical softening can occur, but such eventualities are not common. A more diffuse effect on the hemisphere, particularly on its white centrum, consists in the early deformation (concavity of its dorsolateral surface) due to expression of its fluid content, at times with the occurrence of secondary edema (particularly if the clot is suddenly evacuated when the expression of tissue fluids is quite complete). As illustrated by one of these two cases, it is possible for severe residual lesions to develop in the hemisphere in the form of early softening or late cyst-like defects, with intervening gliosis as a consequence of this mechanism.

The commoner vascular lesions, however, occur in the form of red softening of the basilar and mesial surfaces of the occipital lobe by transitory occlusion of the posterior cerebral artery. This lethal process is facilitated by a herniation of the medial portion of the hippocampal gyrus into the incisura of the tentorium. This same process also compresses the upper brain stem, with tearing of its intrinsic vessels, resulting in hemorrhagic effusions into both basilar and tegmental portions. These hemorrhages into the brain stem undoubtedly constitute one of the major factors

in bringing about the fatal issue in many cases. That they are not always fatal, even when severe, is shown in the two cases here reported, in which the survival period was over six months in each instance.

ALPERS, Philadelphia.

PAIN OF CENTRAL ORIGIN IN MEDULLARY REGION. A. HILFER and J. M. NIELSEN, Bull. Los Angeles Neurol. Soc. **17**:192 (Dec.) 1952.

When the cervical or medullary nucleus of the trigeminal nerve or its descending root is involved by an irritating focus, the patient experiences pain in the face. Two such cases are reported with slowly oncoming vascular occlusion of the affected area. One was a fairly typical case of Wallenberg's syndrome, thrombosis of the right posterior inferior cerebellar artery with its presenting symptom, pain in the ipsilateral part of the forehead. In the second case onset was with severe pain in the left frontal region for one hour, then analgesia of the first division of the left trigeminal nerve and all of the body on the right side below the third cervical level. The patient had a left Horner syndrome and left cerebellar ataxia. The diagnosis was thrombosis of a high cervical (C_3) left spinal artery.

ALPERS, Philadelphia.

CYSTS OF THE SEPTUM PELLUCIDUM. W. McK. CRAIG, R. H. MILLER, and C. B. HOLMAN, Proc. Staff Meet., Mayo Clin. **28**:330 (June 3) 1953.

The authors describe two patients, identical twins, 2 years of age, admitted for study because of mental retardation and convulsions, in both of whom cysts of the septum pellucidum were demonstrated by pneumoencephalography. The cavum septi pellucidi occurs normally about the fourth or fifth month of fetal life, disappearing as the fetus grows. The pneumoencephalograms were characteristic of this condition.

Twenty-four hours after pneumoencephalography, roentgenograms of the head revealed that the cysts had ruptured spontaneously into the ventricular system. Cysts of the septum pellucidum may or may not communicate with the ventricular system. When they do not communicate and ventricular fluid is removed during the making of pneumoencephalograms, thus reducing the pressure in the ventricular system, they may rupture into the ventricular system. Such a rupture occurred in these two patients, eliminating the need for surgical treatment of the cysts.

ALPERS, Philadelphia.

TRAUMATIC EPILEPSY AFTER CLOSED HEAD INJURY. G. PHILLIPS, J. Neurol., Neurosurg. & Psychiat. **17**:1 (Feb.) 1954.

Epilepsy is uncommon after closed head injury. Wagstaffe gave a figure of 2% for its incidence, and reports of later authors vary from 1 to 10%. Phillips studied 2,000 cases of closed head injury from the wartime records of the Military Hospital for Head Injuries, Oxford. Of these, 500 were a relatively unselected group, and the incidence of post-traumatic epilepsy was 6%. One hundred ninety cases of traumatic epilepsy from the entire series are considered in some detail.

The points especially considered were (1) the large number of cases (104) which occur within 3 months of injury, (2) the rapidly decreasing number of cases after 3 months, (3) a period of 6 months in which no fits were seen (from 18 months to 2 years), and (4) the group of late cases after 2 years.

The large group of early cases (less than three months) represented almost 55% of the total 190 cases. Of these 104 patients, 66 had a fit within one month of the injury and 45 of these had the seizure in the first two weeks. In closed head injuries without complication the trauma is maximal at the beginning and its effects presumably decrease as consciousness returns. If trauma is the direct cause of the fit, a seizure should occur at once when the degree of injury surpasses the subject's convulsive threshold. This clearly did not happen in these cases, for the occurrence of a latent interval of varying duration was a very constant feature.

There were 160 cases of general seizures recorded, only 30 of focal attacks. Focal seizures developed earlier than did general seizures. Almost 50% of the focal attacks occurred in the first few days after injury.

In observations on the duration of post-traumatic amnesia (P. T. A.), it was found that about 50% of patients with traumatic epilepsy had a P. T. A. of over 24 hours. In 77% of the short P. T. A. cases the first fit occurred within three months of the injury; in the long P. T. A. group 77% of the first fits appeared after three months. Cases with a long P. T. A. had a higher incidence of epilepsy.

Constitutional factors appeared to be relatively unimportant in etiology. From this evidence, also, there is no reason to suppose that a previous head injury from which a full recovery has taken place will permanently lower the subject's convulsive threshold and render him more liable to seizures after succeeding cranial trauma.

There is little information to be gained from the EEG records in this series of cases. Of the acute cases studied at Oxford, approximately 70% showed some EEG abnormality in the early stages. Fixed epileptiform dysrhythmias with paroxysmal changes in amplitude or frequency were rare and appeared to be confined mainly to the late cases with an incidence delay of over two years. Focal dysrhythmias in closed head injury appeared to be excessively rare and seemed to be restricted to early cases in the primary phase with focal signs or depressed fracture, particularly when the fit was focal or when a general seizure was preceded by a focal motor or sensory aura. In the series of 190 cases with fits, the EEG was quite normal in nearly 30% of the cases in which it was recorded.

The author discusses the possible significance of the varying intervals at which fits develop from the point of view of the etiological factors concerned in traumatic epilepsy.

ALPERS, Philadelphia.

POST-ENCEPHALITIC PARKINSONISM WITH AMYOTROPHY. J. G. GREENFIELD and W. B. MATTHEWS, J. Neurol., Neurosurg. & Psychiat. **17**:50 (Feb.) 1954.

The authors review the histories of two patients with postencephalitic Parkinsonism with oculogyric crises, both of whom developed progressive spinal amyotrophy many years after the onset of Parkinsonism.

The first patient developed Parkinsonism, torticollis, and oculogyric crises 10 years after a presumed attack of encephalitis and, after a further 12 years, a condition clinically indistinguishable from amyotrophic lateral sclerosis.

In the second case the interval between the original attack of encephalitis and the onset of amyotrophy was more than 20 years. The patient died of dysphagia and respiratory embarrassment. A full examination of the brain and spinal cord showed degeneration in the globus pallidus, the pigmented cells of the midbrain and pons, oculomotor nuclei, and anterior horns of the cervical and dorsal enlargements of the spinal cord. There were no tract degenerations.

The authors refer to a number of case reports of a clinical syndrome closely resembling motor neuron disease coexisting with undoubted evidence of chronic encephalitis. They feel that the frequency with which this combination has been reported makes it unlikely that it is a mere chance association of two diseases. The pathogenesis of postencephalitic amyotrophy is discussed.

ALPERS, Philadelphia.

Diseases of the Spinal Cord

OPTIC NEUROENCEPHALOMYELOPATHY (DEVIC'S DISEASE). R. G. SMALL, A. M. A. Arch. Ophth. **50**:368 (Sept.) 1953.

Small reports a case of optic neuroencephalomyelopathy in which there had been a complete remission for over six months. The patient was hospitalized with eye symptoms of bilateral dimness of vision, with general weakness and severe frontal headaches. Iridoplegia developed swelling of both optic nerve heads; light perception was lost in both eyes, and the patient developed profound peripheral manifestations of central nervous system pathology. Because of the optic nerve head swelling craniotomy was done, but there was no evidence of an intracranial neoplasm.

On the fifth hospital day improvement began in the patient, with beginning remission of all symptoms. On the 14th day color vision began to return. On the 16th day the patient was up for the first time and was able to stand, with help. Bowel and bladder control gradually returned. Improvement was sustained, and the patient was discharged on the 26th day after admission. Three months later there was some weakness of the legs, with paresthesias. The patient was able to read fine print and the fundi were normal except for some questionable pallor of the discs. Three months later the patient was seen again. At this time the neurological status was normal.

SPAETH, Philadelphia.

PATHOLOGY OF SPINAL CORD LESIONS AND THEIR RELATION TO THE CLINICAL FEATURES IN PROTRUSION OF CERVICAL INTERVERTEBRAL DISCS. W. G. P. MAIR and R. DRUCKMAN, Brain **76**:70 (March) 1953.

Mair and Druckman present four rather typical cases of ruptured cervical intervertebral discs which were followed to necropsy at Queen Square. The leptomeninges were found to be slightly thickened, with occasional foci of mild perivascular infiltration. The most affected segments of the cords were flattened and showed demyelination of the lateral columns in all cases, and of the anterior part of the posterior columns in three cases. Only one case showed demyelination ventral to the anterior horn, and it also exhibited loss of the axons at the posterior root entry zones and the adjacent part of the cuneate fasciculi. Segments cephalad to the most damaged segment showed ascending degeneration in the periphery of the lateral and posterior columns. In those caudad to the lesion descending degeneration was present in the lateral columns. The gray matter exhibited nerve cell damage and loss, often severe. Three cases did not show degenerative changes in the posterior nerve roots, or in their posterior columns in the distribution of demyelination expected following injury of the posterior nerve roots. The blood vessels in the affected regions were thick-walled, due to fibrosis of the adventitia, and occasionally were surrounded by round cells.

The less damaged portions of the gray matter exhibited chromatolysis and neuronophagia, while the severer lesions showed loss of nerve cells, gliosis, and even cavitation. Changes in the white matter ranged from swelling of the myelin and axons and microglial proliferation to destruction of myelin and axons and glial scar formation. The histological changes were similar to those of ischemia.

It was considered that the lesions of the cord resulted from reduction of blood supply in the distal distribution of the anterior spinal artery, since the compressive force would exert more obliterative effect upon vessels subject to the force over a longer distance. The anterior columns, which were spared, are supplied by shorter proximal branches of the anterior spinal artery. Also, the more distal situation of the fibers to the lower limbs with relation to branches of the anterior spinal artery may explain how weakness often appears earlier in a lower rather than in an upper limb.

JOHNS, New York.

DISSEMINATED LUPUS ERYTHEMATOSUS WITH INVOLVEMENT OF THE SPINAL CORD. P. G. PIPER, J. A. M. A. **153**:215 (Sept. 19) 1953.

Piper reports this case as an illustration of a rare complication of disseminated lupus erythematosus, i. e., vascular involvement of the spinal cord producing an infarct, with resulting paralysis of the lower extremities.

The patient was a 19-year-old white girl who, just prior to her sixth hospitalization for disseminated lupus erythematosus, had experienced numbness and tingling of both lower extremities, which gradually extended up to the trunk with progressive weakness, marked diminution in motility, and difficulty with urination.

Neurological examination of this acutely ill patient showed the reflexes to be generally hypoactive. There was considerable loss of sensitivity to pinprick in the perianal region, and a Babinski reaction was elicited on the left. The patient did not respond to treatment with cortisone and penicillin; the fever continued; she developed generalized twitching and died six weeks after admission.

Previous cases have been reported in which the essential central nervous system lesion was vasculitis with fibrinoid change of the involved vessels and an associated myelomalacia, and occasionally with resulting adhesive meningitis or chronic meningoencephalitis. Although the vessels within the brain proper and the meninges were involved, the most significant alterations in this case were in the blood supply to the spinal cord. The complete postmortem diagnosis was as follows: systemic staphylococcic septicemia with multiple focal septic abscesses; spinal cord swelling and degeneration due to vasculitis, with thrombosis of the vessels supplying the meningeal vessels to the lumbar cord; cerebral hyperemia and minimal vasculitis; bilateral bronchopneumonia; pulmonary edema; arteriolonephrosclerosis; splenomegaly, and multiple septic splenic infarcts.

ALPERS, Philadelphia.

ACUTE DILATATION OF THE STOMACH AS A LATE COMPLICATION OF POLIOMYELITIS. K. K. HUSSAIN, Lancet **1**:282 (Feb. 9) 1952.

Hussain reports on two patients with poliomyelitis who had spent months in respirators and then developed acute dilatation of the stomach. The first patient was a 20-year-old woman who had been in a respirator for seven months, when she developed acute dilatation of the stomach and died in five hours. There had apparently been before death a depression or paralysis of the cranial autonomic nervous system, with enlarged pupils, dry mouth, tachycardia, and the dilatation of the stomach. The gastric distention further displaced the paralyzed diaphragm and increased the pulmonary collapse, causing greater cardiac embarrassment and cerebral anoxia.

The second patient, a 25-year-old woman, had had several attacks of acute dilatation of the stomach and died three days after the last recurrence. These attacks included, in addition to the dilatation, tachycardia which did not respond to pressure on the carotid sinus, dilatation of the pupils, dryness of the mouth and dysphagia, and a poor response to carbachol and neostigmine. These findings suggest paralysis of the connector cells of the autonomic nervous system, especially in the dorsal nucleus of the vagus and the excitor cells of the parasympathetic system in Auerbach's plexus.

The author believes that the virus of poliomyelitis may cause more damage to nerve cells than is at first apparent and that certain apparently intact cells become abnormally vulnerable to oxygen lack. For this reason it is especially important to provide adequate pulmonary ventilation for respirator patients. He points out that the alkali reserve may be used as an index of adequate ventilation.

MADOW, Philadelphia.

FATE OF THE FACE IN POLIOMYELITIS. E. W. MOORE, Lancet **1**:1092 (May 31) 1952.

Moore reports on the degree of recovery a year or more after the onset in 14 cases of facial paralysis occurring in patients with poliomyelitis. Eight of the patients had bilateral complete paralysis of the face, and six had weakness of the lower half of the face only (partial paralysis).

When seen a year or more after the onset, all the patients with partial paralysis had completely recovered from their facial paresis without specific treatment. Recovery had taken from a few weeks up to six months, the patients with the least paralysis recovering most quickly.

Seven of the eight patients with complete paralyses still showed residual weakness, more apparent in the lower half of the face. A variable degree of recovery had taken place, mostly within the first six months. The exception was a boy of 4 years, whose complete facial paralysis had recovered completely within three months.

MADOW, Philadelphia.

DELAYED MYELOPATHY FOLLOWING A FRACTURE OF THE ODONTOID. L. BARRAQUER-BORDAS, L. BARRAQUER-FERRÉ, F. DURAN, A. MODELL, E. TOLOSA, J. TORRUELLA-PAUSAS, and J. M. SEGARRA-OBIOL, Rev. neurol. **89**:193, 1953.

At the age of 5 years a child was thrown off a donkey and sustained a mild injury to her cervical spine. She recovered and had no symptoms except for occasional urinary incontinence during the ensuing years. At the age of 28 she began to notice involuntary jerking of the left upper extremity. There gradually developed weakness of both lower extremities and, within

six months, a quadriparesis. X-rays revealed a fracture of the odontoid with anterior subluxation of the atlas. The spinous process of the axis projected posteriorly. The patient died shortly after laminectomy. Autopsy revealed that the atlas was displaced anteriorly and the axis posteriorly, so that the cord was compressed.

BERLIN, Mount Vernon, N. Y.

Treatment, Neurosurgery

BROMIDES IN THE TREATMENT OF EPILEPSY IN CHILDREN. S. LIVINGSTON and P. H. PEARSON, A. M. A. Am. J. Dis. Child. **86**:717 (Dec.) 1953.

With the enthusiasm for the newer anticonvulsants, bromides are not used very extensively. The authors feel that bromides are still a valuable anticonvulsant. Triple bromides were given to 196 epileptic children with severe organic brain lesions as evidenced by mental retardation or gross neurological deficits. About half of the group had previously been treated with other anticonvulsants, without success. The other half had received no previous treatment. The period of observation was longer than two years.

Type of seizures included grand mal (generalized or focal), minor motor, simple petit mal, and psychomotor varieties. In 31% of the patients the seizures were completely controlled, and in an additional 20% the seizures were reduced to less than one-fourth their previous frequency. A good therapeutic effect was obtained when the blood bromide concentration ranged between 14.5 and 24.3 mEq. per liter (116 and 194 mg. per 100 cc.). Infants and children tolerate bromides well. Drowsiness and acneform skin eruptions were the only untoward reactions, the latter seen only in adolescence. Bromides possess a wide margin of safety.

SIEKERT, Rochester, Minn.

LIMITATIONS IN THE USE OF GAMMA GLOBULIN IN POLIOMYELITIS. W. McD. HAMMON, Am. J. M. Sc. **226**:125 (Aug.) 1953.

Hammon reports that hundreds of thousands of injections of gamma globulin must be given to provide protection for one or two subjects because of the difficulty of ascertaining the subjects needing immunization. Under only one set of ideal circumstances, perhaps 1 of each 250 to 300 patients receiving gamma globulin derive any benefit. Under other favorable circumstances, perhaps in 1 case for each 2,000 injections, the infection was prevented by injection of gamma globulin. In 12 children with an onset within one week after the injection, no case had significant sequelae. It seems more rational to administer gamma globulin during the early period of infections suspected of being poliomyelitis in order to modify the disease rather than to resort to wholesale immunization of large segments of the population.

BERLIN, Mount Vernon, N. Y.

SOCIOPSYCHOLOGICAL TREATMENT OF EPILEPSY. W. G. LENNOX and C. H. MARKHAM, J. A. M. A. **152**:1690 (Aug. 29) 1953.

Lennox and Markham point out that in the treatment of epilepsy today the good physician must match modern drug and surgical therapy with practical sociopsychological therapy. The emotional reactions aroused by epilepsy are not confined to the person seized. They are communicated to his family and friends, often in exaggerated forms.

The physician's treatment of emotional and social handicaps involves two fields. The first is personal contact with the patient and his family and friends. The second contribution is correction of the public misunderstanding of epilepsy and revision of laws that discriminate unfairly. The authors discuss such problems as present immigration laws, education, marriage, and employment as they affect the patient suffering with epilepsy.

The authors' experience with 43 epileptic physicians, as part of a much larger group, is reviewed. In so far as is known, only one physician has had to abandon the practice of medicine because of his seizures. Five have made the study and treatment of epilepsy their life interest.

A plea is made that the physician treating epileptics be well informed concerning epilepsy and genuinely interested in the patient and his problem, and that ignorance, prejudice, and fear concerning the disease be dispelled.

ALPERS, Philadelphia.

TREATMENT OF DYSTROPHIA MYOTONICA WITH ACTH. O. GARAI, J. Neurol., Neurosurg. & Psychiat. **17**:83 (Feb.) 1954.

Garai reports four cases of dystrophia myotonica treated with corticotropin. In this group the only real effect seemed to be on the myotonia. Thus, the patient showing the best response was one in whom the myotonia was particularly marked and the dystrophic process less in evidence. Those others in whom wasting, weakness, and dystrophic features dominated the picture showed little response to treatment.

Garai offers no explanation of the mode of action of corticotropin but suggests further study of its effect on muscle potassium, since other work on potassium in physiological processes has given valuable leads.

ALPERS, Philadelphia.

STATUS OF 78 PATIENTS TREATED WITH PSYCHOSURGERY ONE YEAR AFTER OPERATION. M. DAVID, J. SAUGET, H. HECAEN, and J. TALAIRACH, Rev. neurol. **89**:1, 1953.

In this group of patients the authors performed 2 topectomies, 14 undercutting procedures, and 62 lobotomies. There were 6 cases of manic excitement, 6 of depressions, 4 of chronic delirium states, 11 of neuroses, 47 of schizophrenia, and 4 of character disorders with epilepsy. In the group of psychotic patients, 8 were reported as cured, 10 improved, 10 in remission, and 31 as unimproved after one year. The four patients with chronic delirium states were unchanged. Four epileptic patients had lobotomies because of behavior disorders characterized by impulsivity and agitation of such severity that they had to be institutionalized. All benefited from the procedure, although one patient became extremely passive. The seizures were not worsened. The authors cite the work of other surgeons, who have treated a total of 29 epileptic patients with lobotomy or pericallosal topectomy, with improvement of the behavior disturbance in all but 5. In eight patients who had pericallosal topectomies the frequency of seizures diminished.

BERLIN, Mount Vernon, N. Y.

News and Comment

RESEARCH GRANTS, NATIONAL INSTITUTE OF MENTAL HEALTH

Twenty-five new research grants recently were awarded by the Surgeon General of the Public Health Service upon the recommendation of the National Advisory Mental Health Council at its June meeting. The announcement includes the names of the principal investigators for each project, their location, the subject of the study, the period for which the project is approved for grant support, and the amount awarded for the first year. The 25 new grants awarded total $373,178.

Anderson, John E., and Harris, Dale B. University of Minnesota. The relation of childhood behavior to adjustment in adulthood. Three years. First year $14,796.

Bandura, Albert. Stanford University. Relation of therapeutic competence to personality of psychotherapist. One year $1,851.

Blocksma, Douglas; Fox, Robert, and Lippitt, Ronald. University of Michigan. A study of methods for improving social acceptance and participation of rejected children. Three years. First year $27,972.

Blom, Gaston E., and Long, Robert. Massachusetts General Hospital. Study of emotional factors in children with rheumatoid arthritis. Four years. First year $17,981.

Busse, Ewald W. Duke University. Effect of aging upon the central nervous system. Two years. First year $14,534.

Cohen, Louis D. Duke University. The assessment of change in anxiety level. One year $5,400.

Dean, John F., and Williams, Robin M., Jr. Cornell University. Social and cultural factors in adjustment of American women. One year and a half. First year $10,770.

Drake, Miles E. Vineland State School. Metabolism of phenylpyruvic acid in mental deficiency. Three years. First year $15,869.

Fink, Maximilian. Hillside Hospital, New York. Perceptual changes induced by drugs and electroshock. Two years. First year $9,612.

Gerty, Francis J.; Garner, Ann Margaret, and Wenar, Charles. University of Illinois College of Medicine. Studies of psychosomatic disorders in children. Two years. First year $22,396.

esses. Two years. First year $14,018.

esses. Two years. First year $14,018.

Harlow, H. F. University of Wisconsin. Symposium on interdisciplinary research in the behavioral, biological, and biochemical sciences. One year $8,910.

Landis, Carney. Research Foundation for Mental Hygiene, Inc., New York State Psychiatric Institute. Sensory and motor tests of CNS efficiency. Three years. First year $21,956.

Lauer, Donald W. Indiana University. Response variables in classical conditioning. Two years. First year $8,760.

Ledwith, Nettie H. Pittsburgh Child Guidance Center. Rorschach responses of elementary school children. One year $9,720.

Loeb, Martin B. Community Studies, Inc. Interaction patterns in a psychiatric hospital. One year and a half. First year $20,262.

Nulsen, Frank E., and Crocker, David. University Hospitals. Evaluation and treatment of chronic pain. Two years. First year $5,972.

Pavenstedt, Eleanor, and Greeley, David McL. Boston University School of Medicine. The effect of maternal maturity and immaturity on child development. Two years. First year $36,085.

Phillips, Leslie. Clark University. The application of developmental theory to problems of social adaptation. Three years. First year $16,102.

Riley, John W., Jr. Rutgers University. Analysis of small group and interpersonal relations. Three years. First year $13,859.

Rogers, Carl R. University of Chicago. The process and facilitation of personality change. Three years. First year $40,000.

Sawrey, William L. University of Colorado School of Medicine. Role of psychological factors in production of gastric ulcers. Two years. First year $8,817.

Semrad, Elvin V., and Greenblatt, Milton. Harvard College. Relation of social interaction process and clinical changes to outcome of psychotherapy. One year $11,930.

Stellar, Eliot. University of Pennsylvania. Experimental study of the behavior of the marmoset. Two years. First year $4,644.

Wallace, Anthony F. C. University of Pennsylvania. Mental health aspects of cultism. Two years. First year $10,962.

This list does not include grants awarded to investigators for the continuation of projects previously supported by this Institute. Forty-two such grants, totaling $569,393, were also awarded at the June meeting.

CONGRESS OF NEUROLOGICAL SURGEONS

A meeting of the Congress of Neurological Surgeons will be held at the Waldorf Astoria Hotel, New York, on Nov. 4, 5, and 6, 1954.

Dr. Kenneth McKenzie, of Toronto, will be the honored guest and deliver papers entitled "Brain Tumor with Special Reference to Acoustic Neuroma and Benign Gliomas," "Experiences with Sympathectomy for Vascular Hypertension and Leukotomy for Mental Disturbance," and "Spasmotic Torticollis, Ménière's Syndrome, and Results Following Tractotomy for Trigeminal Neuralgia."

Symposiums on Cervical Trauma by Dr. Frank Mayfield, Cincinnati, and Dr. Howard Rusk, New York, will be followed by a panel discussion with Dr. Thomas Hoen, Dr. K. G. McKenzie, Dr. Francis Grant, Dr. J. Lawrence Pool, Dr. I. M. Tarlov, Dr. Bronson Ray, Dr. John E. Scarff, Dr. L. M. Davidoff, Dr. Lester Mount, Dr. E. Jefferson Browder, and Dr. C. G. de Gutiérrez-Mahoney.

A panel discussion on the Medico-Legal Aspects of Head Injuries will be moderated by Dr. A. Earl Walker, of Johns Hopkins University, and will include Dr. William Caveness, Dean Roscoe L. Barrow, of the University of Cincinnati College of Law, and Mr. W. Scott Allan, of the Liberty Mutual Insurance Company.

DR. WARTENBERG HONORED BY VIENNESE SOCIETY FOR PSYCHIATRY AND NEUROLOGY

Prof. Robert Wartenberg, of the University of California Medical School at San Francisco, at present visiting Professor of the University of Freiburg i. Br., has been elected Honorary Member of the Viennese Society for Psychiatry and Neurology.

AMERICAN PSYCHOSOMATIC SOCIETY

The American Psychosomatic Society will hold its Twelfth Annual Meeting at the Claridge Hotel, Atlantic City, N. J., on Wednesday and Thursday, May 4 and 5, 1955. This meeting will be immediately preceded by those of the American Society for Clinical Investigation and the Association of American Physicians. It will be followed by the meeting of the American Psychoanalytic Association.

The Program Committee would like to receive titles and abstracts of papers for consideration for the program no later than Dec. 1, 1954. The time allotted to the reading of each paper will be 20 minutes. The Committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all of the medical specialties, and in contributions in psychophysiology and ecology.

Abstracts for the Program Committee's consideration should be submitted in duplicate and should be sent to the chairman, Dr. Lawrence S. Kubie, 551 Madison Ave., New York 22.

RESEARCH GRANTS, NATIONAL INSTITUTE OF MENTAL HEALTH

Grants to investigators in the field of mental health were initiated in 1953-1954 upon recommendation of the National Advisory Mental Health Council to assist in the opening of research careers to qualified young psychiatrists and scientists in related disciplines. The intent of the new program is to enable a number of highly qualified young men or women to spend from three to five years in full-time research.

Awards have already been made this year to the following individuals to conduct research in the problems indicated:

Peter H. Knapp, M.D., Boston University School of Medicine
"Emotional and Physiological Relationships in Various Disease Processes": Five years

Enoch Callaway III, M.D., University of Maryland School of Medicine
"Relation of Autonomic Activity to Perception": Five years

Henry Lesse, M.D., Tulane University of Louisiana School of Medicine
"Correlation of Electrical Brain Activity with Thought Processes": Five years

The closing date for receipt of applications for a mental health career investigator grant for the coming year is November 1. Information and application blanks may be obtained from the Research Grants and Fellowships Branch, National Institute of Mental Health, Bethesda 14, Md.

CORRECTION

In the article by Drs. Geraldine King, Harry W. Slade, and Francisco Campoy, "Bilateral Intracranial Aneurysms," in the March, 1954, issue of the ARCHIVES, Reference 7 (p. 335) should read: Fearnsides, E. G.: Intracranial Aneurysms, Brain **39**:224-296, 1916. In line 8, page 326, "and Cantab" should be omitted.

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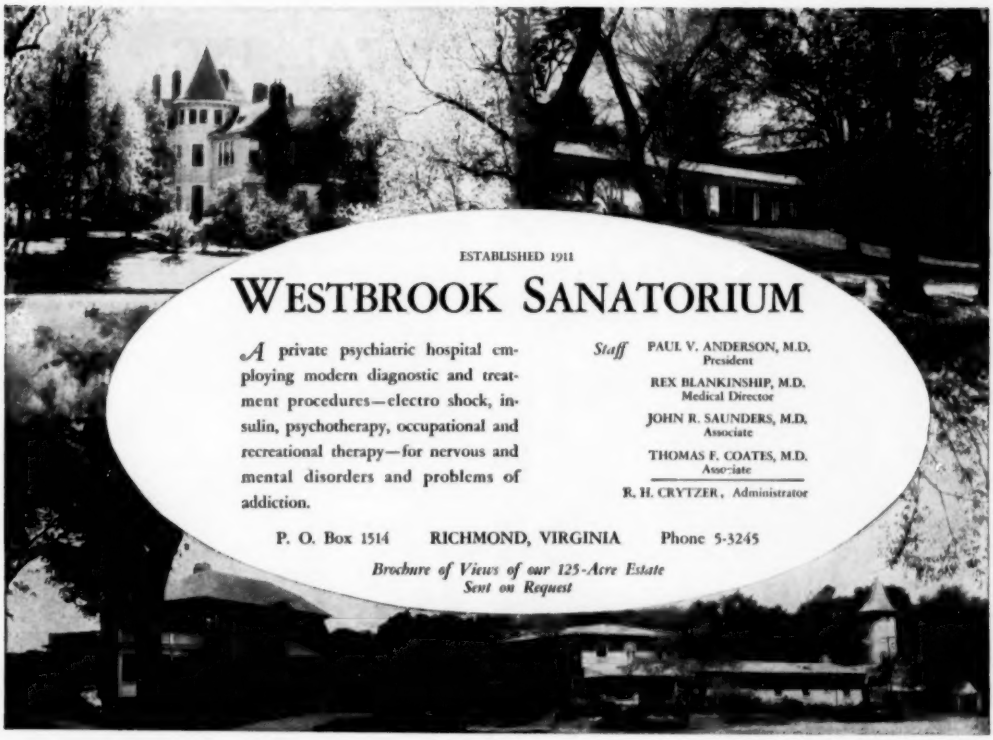
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1. Gerhard Hirschfeld and Joseph Bell *Diseases of the Nervous System* **12**: 3-7, September, 1951.
2. Gerhard Hirschfeld *Journal of Nervous and Mental Diseases* **117**: 323-328, April, 1953.
3. W. T. Liberson *Psychiatric Treatment* Vol. 31 of Proc. A.R.N.M.D. Williams and Wilkins, Baltimore, 1953.

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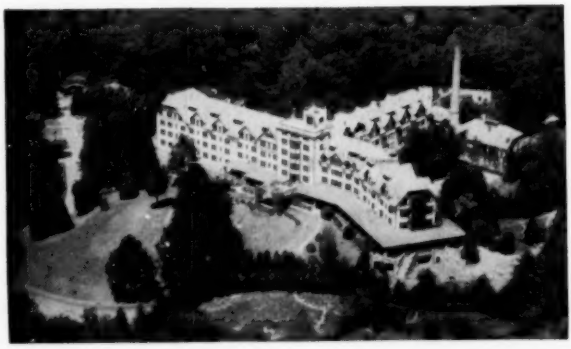

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